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TITLE: Studies of Tissue Perfusion Failure at LAC+USCMC and the Incorporation of the Results into a National Trauma Database

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14. ABSTRACT

The goal was to produce a comprehensive, objective, unbiased database that can be independently mined by members of the combat-casualty-care community to identify patients who are at risk in the earliest stage of the therapeutic process, adjust therapies to improve outcomes, and promptly determine whether the new therapy will lead to survival.

A retrospective database was constructed with emphasis on early time hemodynamic studies of patients with severe trauma. Data on a total of approximately 740 patients seen at our institution were combined in an easily accessible format from three mini-databases: prehospital (Department of Health Services data), Emergency Room, and ICU. The combined deidentified data on the 732 patients was delivered to the US Army Institute for Surgical Research in Fort Sam Houston, Texas, on July 27, 2005.

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Table of Contents

1. Introduction

In this project, we assembled a large database of trauma victims by linking data from three databases generated at Los Angeles County+USC Medical Center (LAC+USC). These contain physiologic data acquired from the field through the intensive care unit and discharge. The large database can be independently mined by members of the combat-casualty-care community. As it is comprehensive, objective and unbiased, the database is expected to provide insight into the resuscitative outcome of combat casualties and civilian trauma victims. Data mining could address such questions as a) when it is necessary for a medic on the battlefield to resuscitate a trauma victim, b) how the effectiveness of the resuscitation effort can be measured objectively with outcome predictors, and c) what is the desired end point of resuscitation: can it be defined empirically by the survivors' values?

The project initially had a different emphasis (see 2.3 below) but was changed by the Contract Reporting Officer to consist of supplying the large database in a usable format.

This was initially a three-year project beginning October 1, 2001, to end September 30, 2004. We received funds for the first two years only.

2. Body

2.1 Summary of the Study

The large database (the Main Project Database) consists of subsets of three databases that contain data on a group of 732 trauma patients from the field through their ICU stay and discharge or death.

The three databases are, in temporal sequence:

a) Los Angeles County Department of Health Services prehospital data (from the field to the LAC+USC Emergency Room). We call this the Trauma Registry, because the data is compiled by trauma nurses at LAC+USC. The data we segregated for the Main Project Database is a small subset of the entire Trauma Registry.
b) Noninvasively monitored data on the 732 trauma patients from the LAC+USC Emergency Room to the operating room or surgical intensive care unit (SICU). This is called the "WCS database."
c) Electronically generated data (from the SICU computer) on those WCS patients who went to the SICU. The data we segregated for the Main Project Database is a small subset of the entire SICU database.

The WCS database contains the fewest patients, and thus was the limiting factor in creating the Main Project Database. The WCS database began collecting data in 1996 and continued under this award through mid-2002.

Our original plan was for a subcontractor, Geospace Research, to integrate data on the WCS patients from the three databases and analyze it using algorithms designed to predict outcome. Only afterward would we send the Main Project Database to the Army.

During Year I, LAC+USC personnel sent a sampling of WCS data and associated data from the other two databases to Geospace for initial work on algorithms.

However, during Year I and Year II, change requests from the Army and issues relating to the new HIPAA regulations as well as issues regarding the consent process delayed the funding and the performance of this work (see Appendix A).

After numerous meetings with Army sponsor representatives , our deliverables were changed (see Section 2.2.1). We were told by the sponsor that supplying data on the 732 patients from the three deidentified databases in easily accessible form would be adequate to fulfill the

terms of the contract. (Personal communication, Belzberg and Convertino). Army researchers would then create their own algorithms.

In light of the changes to our deliverables, and the difficulties in interfacing with Geospace, we terminated the Geospace contract after one year. However, we continued to collect data into the WCS database under a separate IRB approval. We assembled and deidentified the data on the 732 patients at LAC+USC in 2005.

On July 26, 2005, we sent a computer disc containing the deidentified Main Project Database along with glossaries and explanatory material to researchers at the U.S. Army Institute of Surgical Research (See Appendices B.1-B.7 for glossaries and samples of the data).

2.1.1 Timeline summary

During Year 1 (2001-2002) we purchased computers and database software for LAC+USC and Geospace. We collected patients into the WCS database. Geospace began creating a "toy" or model database integrating data from all three databases.

However, because of several change orders from our Army sponsor representative, we stopped work on the study from approximately September 2002 to October 2003 while seeking IRB approval and conformance with HIPAA regulations. (see 2.2.1 below)

During Year II (October 2002- September 2003), while waiting for clarification, we continued to pay project staff at LAC+USC. During Year II, collection into the WCS database continued. In October 2003, we received IRB approval to include data collected from September 2001 to September 2002 to the project, which initially had covered only data prior to September 2001).

During Year III (October 2003- September 2004), we did not work on this project except to maintain its status with the IRB and continue discussions with Army researchers on the future direction of the work.

Subsequent to Year III (in 2005) we packaged and delivered the Master Project Database to the Army.

2.2 Changes in planned research activities and Statement of Work

In the period since the Year II annual report, there have been major changes in the goals, objectives and execution of this project. These changes involve:

1. Redesign of the database and analytic functions
2. Major alteration of timeline
3. Change in reporting structure

2.2.1 Change in Statement of Work

Our original Statement of Work focused on consolidating two existing databases, adding data to it in real-time, adding data using new sensors (during Years 2 and 3), and developing and testing algorithms for prediction of outcome.

Abstract of our original Statement of Work

> Year 1: Two LAC+USCMC relational databases will be consolidated into a new integrated database to make data mining very efficient. We will develop a set of new procedures that will allow future trauma cases to be seamlessly added to the database. During the first year, the existing database containing physiologic parameters will be used as a tool to evaluate and predict the outcome of critically injured patients.

Year 2: New sensors will become available in Years 2 and 3 . Appropriate data acquisition and display systems will be added as needed to monitor patient status in real time and to record sensor outputs for inclusion into the database. The evaluation of the new sensors will require informed consent of the patients undergoing study. A user-friendly graphical viewer will be developed so that the data are accessible to users other than computer specialists.

Year 3: Work on the database will focus on the maintenance of the system as new case histories are added and new sensor data are included. In addition, the relational operations available to the nonspecialist for probing the database will be expanded. Changes in the database access program will also be made based on feedback from the Year 2 users. Studies involving new noninvasive sensors and new fluid therapies will continue, and new sensors and sensor combinations will be evaluated for their contribution to the prediction model.

Beginning in 2001, however, our Contract Reporting Officer, Jaques Reifman, directed us away from predictive modeling and the use of additional novel sensors. He directed us to focus on creation of an integrated database containing data both collected prior to the onset of the project (October 2001) and during the three years of the project.

Our initial Statement of Work intended to create a database that other investigators could add to by using their own sensors on their own patients. Dr. Reifman directed us to create a database populated only by our own patients. Our initial Statement of Work required the integration of only the WCS and SICU databases. Because of the change in project design we added data to the Main Project Database from the Trauma Registry (prehospital) database.

We now directed our activities to collecting data on critically ill patients and placing it in a simplified format that could be analyzed by investigators elsewhere. This change made our efforts to construct a toy database obsolete (see Section 2.3.2 below). The Main Project Database was now to be provided to researchers at the U.S. Army Institute for Surgical Research in Fort Sam Houston, Texas.

2.2.2 Major alteration of timeline

During the 2002 ATACCC (Advanced Technology Applications for Combat Casualty Care) meeting in St. Petersburg, Florida, we were told by Dr. Reifman that funding for the project was suspended pending approval by the Army's Human Subjects Research Review Board (HSRRB). The process for obtaining this approval was severely confounded by the passage of new federal legislation under the HIPAA programs. The difficulty in determining how these legislative actions impacted human research funded by the military led to a delay of over one year. In addition to the delays in obtaining clarification from the HSRRB, there were significant delays in obtaining approval from our institution's Institutional Review Board (IRB) regarding the operational definition of prospective and retrospective data. Further difficulties were encountered regarding the method of de-identification of the patients in the databases to be provided to the Army. Each of these issues led to a delay of 3 to 6 months due to the need to interpret new regulations and coordinate approvals from both the HSRRB and our IRB. We received approval from our IRB in October 2003 to include patients collected between September 2001 and September 2002, and at that point we were able to begin work again.

2.2.3 Change in reporting structure

In response to communication difficulties between the investigators and Dr. Reifman, a meeting at Fort Detrick which included Colonel Robert Vandre, the contracting authority, and

others was held in winter 2002-03. We were then instructed to report to the Army research group in San Antonio. As a result of this meeting, we were instructed to continue to process data collected during the study period once we had obtained approval by both the Army's HSRRB and our IRB.

2.3 Details of the study

2.3.1 Summary of the three databases

Our initial Statement of Work indicated that we needed to combine data from only two databases: the William C. Shoemaker (WCS) database and the LAC+USC SICU database. However, once our work plan was changed to the provision of a database from field to discharge, we decided to include data from a third database, the Los Angeles County Department of Health Services Trauma Registry (TR). The TR contains includes prehospital, admission and discharge data obtained by paramedics and Emergency Department personnel, and supplemented after discharge with data entered by dedicated trauma registry nurses. It provides valuable post-discharge information (location discharged to such as home, skilled nursing facility, jail, other hospital).

The TR's role at the hospital is to improve the efficiency of the trauma care system [Ref. 1]. The TR is a relational database in DBF format which we converted to Microsoft Excel prior to delivery to the sponsor.

The WCS database tracks patients beginning with resuscitation in the emergency department through radiology or operating room (if applicable). Between about 10 and 30 physiological parameters are recorded for each of 732 individual patients from 1996 to 2002. Most measurements are noninvasive and the quality of these data is very high. The catalog of WCS parameters has evolved because of the introduction of new noninvasive sensors after 1996, and each of the five WCS substudies measured a slightly different set of physiological parameters. However, the database is anchored by a set of common parameters. The WCS database was provided to the sponsor as a single Excel spreadsheet.

The SICU database provides a comprehensive electronic record of all customary diagnostic measurements, procedures and therapies. The SICU database is a relational database in a proprietary object-oriented database (Eclypsis) transformed for us by an Eclypsis programmer into Microsoft Excel.

The three databases are linked by a patient Study ID number to comprise the Main Project Database. See Appendix B.1 for a graphic description of the structure of the Main Project Database.

2.3.2 Year I work: Construction of a toy database

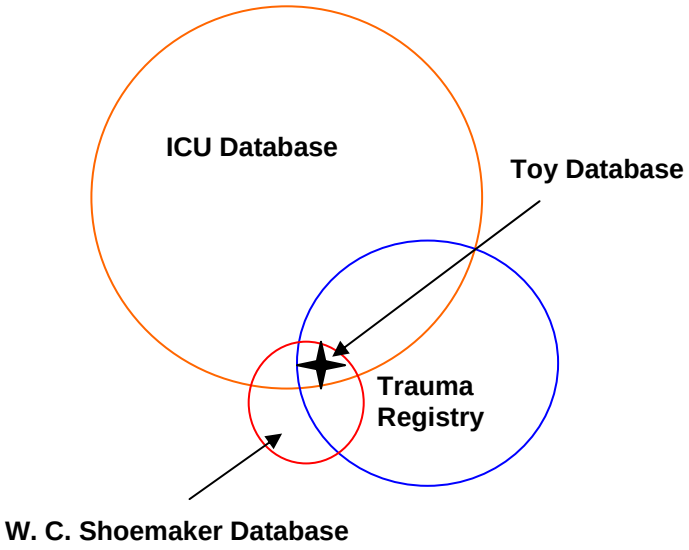
Because of the above-described change in work plan, the toy database is now obsolete. However, we include its description here to explain our Year I effort.

> During Year I, a test data set referred to as the "toy database" was constructed. It consisted of small portions of the WCS database, the SICU database, and the TR database. The toy database was assembled to test the practicability of combining the three diverse databases.
>
> For the SICU database, the number of extracted parameters was limited to ~30. Approximately 24 parameters were extracted from the TR, and all data from a portion of the WCS database (the WCS Heart Rate Variability [HRV] study) were included.
>
> The WCS database takes the form of entries in Microsoft Excel spreadsheets. Both the SICU and TR databases are relational in nature and are hosted by two different database programs, Sybase and Foxbase, respectively. The objective behind assembling the toy database was to identify problems involved in the consolidation of these three data sets.

The ICU database is by far the largest; it is 50 to 100 times larger than the WCS database. The TR is in itself a very large database, but the amount of data/information that is extracted for individual trauma patients is approximately equal to the corresponding patient file sizes in the WCS database. Data dictionaries had to be developed for all three data sets because they had never been used outside of their targeted application. Figure 1 below illustrates the intersection of the three databases; the area with the star represents the data records that became part of the toy database. A total of 53 patient histories were common to all three data sets (WCS, SICU, and the TR). These were merged together into a single database using the Sybase Anywhere 8.0 database program. This new test database was probed and queried primarily with SQL commands to verify that it was properly ordered and complete.

It was found that a considerable effort is involved in sorting and bringing large quantities of diverse data from the SICU database into the main Sybase database. In addition, there is a strong preference for data obtained at the earliest times following patient admission at LAC+USC. The SICU data typically begins 6 to 24 hours after admission, whereas the WCS data begins at admission. As a result, our initial efforts focused on merging the WCS database and the TR database into a single project database. This allowed the early-time hemodynamics of trauma patients to be examined in detail during the first grant year. At the request of the Government, all relevant comments (i.e. character strings) in the WCS data sets were parsed so that they could be readily interpreted as part of the Main Project Database. This was a significant task involving the parsing of more than 50,000 comments.

Figure 1. Data for the Toy Database was extracted from the intersection of three large data sets.



Because the WCS database was in the form of multiple Microsoft Excel spreadsheets, a series of data set transformations was performed to convert it to relational format. To facilitate this process and to trap errors, each cell of the WCS spreadsheet was initially examined with the aid of a Visual Basic program. The program identifies cells that are improperly formatted (i.e.. as a text string instead of a numeric value) and examines all data to make sure that parameter values fall within reasonable limits. If a data value is suspect, the problem was addressed using the original data records of W. C. Shoemaker to resolve the issue. Formatting errors prevent the translation of the Excel spreadsheet into Sybase, and it is much easier to identify them in Excel rather than through terminating errors in the translation programs. Excel formatting errors are often subtle; a text string of “10” is indistinguishable from the numerical value of 10 when viewed in the spreadsheet.

The TR and the SICU databases were supplied as relational databases, so formatting is not an issue. However, the TR database structure does change with time. Both the TR database and the corrected WCS database are imported into the database program in the form of tables.

Data in these "source tables" are never changed or edited. Instead, SQL macros were used in conjunction with the tables to create intermediate data tables. When new TR and/or WCS and/or SICU data is added to the system, new data sets are generated, and analyses are performed to determine whether parameter values are reasonable and whether overlapping data are consistent. For example, parameter distribution functions are examined, survivor/non-survivor values are cross referenced, and hard filtering limits are placed on some parameter values (e.g., blood alcohol level). It is also worth noting that a patient may show up as a survivor in the WCS database, and a non-survivor in the TR. In this case, the patient may have been followed for two weeks for the WCS database and determined to be survivor. However, on occasion patients subsequently undergo sudden downturns and do not survive. When an inconsistency is identified, an investigation must be launched to resolve the problem. This may involve locating a patient's archived medical chart, which can involve a search lasting several days.

For the toy database, a Visual Basic program was written to examine each cell of the WCS Excel sheet for correctness of data format and to determine whether data values were in range. This procedure helped identify errors and made the transformation of the Excel Sheets to database tables easier. Ultimately, SQL queries of the data sets within the Sybase program were used to determine whether unreasonable or inconsistent information was contained in the WCS and TR data sets. In the case of the WCS data set, the records of W. C. Shoemaker were used to verify the data.

2.3.3 WCS database

Table 1 shows data from the five substudies that comprise the WCS database. [Refs. 2-7]. The total number of enrolled patients is 732 rather than 737, because five patients were entered into two of the substudies.

Table 2 shows the percentage of patients covered by various physiological parameters. The first 17 parameters in Table 2 are standard quantities in the WCS database for assessing blood flow and tissue perfusion. The standard non-invasive diagnostics of hemodynamics include electrical bioimpedance measurements of cardiac output, pulse oximetry, and transcutaneous measurements of oxygen and carbon dioxide tension. A brief description of each of these diagnostics is provided below in Tables 3 and 4. Greater detail may found in Ref. 2 and Ref. 8. Four of the five Shoemaker substudies (Heart Rate Variability Protocol and the Surgical ICU 2, Surgical ICU 3, and Pentaspan studies) made use of a special-purpose instrument (ANS-R1000, Ansar Inc., Philadelphia, PA) that measures heart rate variability parameters: L(mean), R(mean), L/R(mean), and HR(mean).

Table 3 lists the medications, blood component therapies, resuscitation fluids, and procedures in the WCS database.

Table 4 provides definitions of the parameters in Tables 1-3**.**

The following explains how the physiological parameters were obtained:

Bioimpedance Measurements. A thoracic bioelectric impedance device (Yantagh, Inc., Bristol, PA) is usually applied shortly after arrival of the patient in the emergency department. Noninvasive disposable pre-wired hydrogen electrodes are positioned on the skin, and three EKG leads are placed across the precordium and left shoulder. A 100 kHz, 4 mA alternating current is passed through the patient's thorax by the outer pairs of electrodes. The voltage is sensed by the inner pairs of electrodes, which capture the baseline impedance (Z_0), the first derivative of the impedance waveform (dZ/dt), and the EKG. The EKG and bioimpedance signals are filtered with an all-integer-coefficient technology to decrease computation and signal processing time. The signal processing algorithm uses a time-frequency distribution (modified Wigner Distribution) analysis that increases the signal-to-noise ratio. Previous studies have documented satisfactory correlation between thermodilution and bioimpedance cardiac output values in trauma patients [Ref. 9].

Pulse Oximetry. Routine pulse oximetry (Nellcor, Pleasanton, CA) is used to continuously assess arterial oxygen saturation ($SapO_2$). Values are observed and recorded at the exact time of cardiac index measurements. Appreciable or sudden changes in these values are noted and confirmed by *in vitro* arterial oxygen saturation obtained via standard blood gas analysis [Ref. 9].

Transcutaneous oxygen and carbon dioxide tensions. Standard transcutaneous oxygen tension ($PtcPO_2$) measurements (Novametrix Medical Systems, Inc; Wallingford, CT) are made continuously throughout the observation period. Values are noted and recorded at the exact times of cardiac output measurements. The measurement system uses the same Clark polarographic oxygen electrode routinely used in standard blood gas analyses. The oxygen tensions are determined in a representative area of the skin surface heated to 44 C to increase diffusion of oxygen across the stratum corneum and to avoid vasoconstriction in the local area of the skin being measured.

Previous studies demonstrated the capacity of $PtcO_2$ to mirror tissue oxygen tension [Ref. 10]. $PtcO_2$ has been shown to reflect the delivery of oxygen to the local area of skin; it also parallels the mixed venous oxygen tension except under late or terminal conditions where peripheral shunting leads to high mixed venous hemoglobin saturation values [Ref. 10]. Although oxygen tension of a segment of the skin does not replicate the state of oxygenation of all tissues and organs, it has the advantage of being the most sensitive early warning tissue of the adrenomedullary stress response. Vasoconstriction of the skin is an early stress response to hypovolemia and other shock syndromes.

Transcutaneous CO2 ($PtcCO_2$) monitoring of the skin surface is performed with the standard Stowe-Severinghaus electrode ((Novametrix Medical Systems, Inc; Wallingford, CT).

Heart rate variability measurements. Heart rate (HR) variability and respiratory rate (RR) variability are measured by spectral analysis techniques with the ANS-R1000 instrument. These parameters are indicative of autonomic nervous activity. The spectral areas of variability are divided into low frequency areas, L(mean), and high frequency areas, R(mean). The L(mean) area extends from 0.04 to 0.10 Hz. This area reflects primarily the tone of the sympathetic nervous system as mediated by the cardiac nerve. R(mean), also referred to as the respiratory area, corresponds to a 0.12 Hz-wide frequency interval centered on the fundamental respiratory frequency. It is indicative of vagal outflow reflecting parasympathetic nervous system activity. The L/R ratio reflects the balance between the sympathetic and parasympathetic nervous systems. [Ref. 4] indicates that a consistently positive relationship exists between HR variability and L(mean) during sudden surges in autonomic activity. This relationship holds to a lesser degree with R(mean). Heart rate variability that reflects autonomic activity is associated with increased MAP, CI, and HR, but decreased tissue perfusion as indicated by the $PtcO_2/FIO_2$ ratio.

Table 1. W. C. Shoemaker Data (Five groups of patients)

Study Name: Fluid Resuscitation Protocol
Focus: Effectiveness of resuscitative fluids on tissue perfusion.
Number of Patients: 319, 78 non-survivors, 24.5% non-survivors
Earliest Admission Date: 7/27/96 (patient 1)
Last Admission Date: 3/25/99 (patient 333)
Recorded Parameters and Percentage of Patients Covered by Measurement

CItd	CIbi	HR	MAP	SapO2	PtcO2	PtcCO2	FIO2	SaO2
25.2	95.8	95.8	94.3	94.0	92.8	92.8	94.9	59.2

SvO2	HCT	DO2I	VO2I
16.5	60.7	59.5	16.5

Study Name: Heart Rate Variability Protocol
Focus: Non-invasive measurements of autonomic nervous system. Heart rate variability and respirator activity.
Number of Patients: 179, 43 non-survivors, 24.0% non-survivors
Earliest Admission Date: 8/18/99 (patient 1)
Last Admission Date: 10/14/00 (patient 179)
Recorded Parameters and Percentage of Patients Covered by Measurement

COtd	COrb	STAR	CObi	CIbi	HR	MAP	PtcO2
56.4	20.7	20.7	91.1	91.1	96.6	96.6	91.6

PtcCO2	FIO2	tcO2/F	SapO2	L(mean)	R(mean)	L/R(mean)	HR(mean)	PaO2	SaO2
91.6	96.6	91.6	96.6	97.8	98.9	99.4	100.0	77.7	77.7

SvO2	HCT	DO2I	VO2I	Qs/Qt
46.4	77.7	49.2	45.3	43.0

Study Name: Surgical ICU 2
Focus: Comparison of invasive and non-invasive measurements on a periodic basis.
Number of Patients: 67, 16 non-survivors, 23.9% non-survivors
Earliest Admission Date: 10/25/00 (patient 1)
Last Admission Date: 5/31/01 (patient 67)
Recorded Parameters and Percentage of Patients Covered by Measurement

COtd	COrb	VCO2	ETCO2	Pox	STAR	TV	RR
67.2	25.4	25.4	25.4	25.4	25.4	55.2	40.3

CObi	CIbi	Zo	dZdT	HR	MAP	PtcO2	PtcCO2	FIO2
98.5	98.5	3.0	4.5	100.0	100.0	92.5	92.5	100.0

tcO2/F	SapO2	L(mean)	R(mean)	L/R(mean)	HR(mean)	PaO2	SaO2	SvO2	HCT
100.0	98.5	11.9	11.9	11.9	4.5	76.1	76.1	52.2	76.6

DO2I	VO2I	Qs/ Qt	BE	PEEP	CVP
55.2	52.2	52.2	56.7	50.7	38.8

Study Name: Surgical ICU 3
Focus: Comparison of invasive and non-invasive measurements on a periodic basis.
Number of Patients: 108, 21 non-survivors, 19.4% non-survivors
Earliest Admission Date: 3/11/01 (patient 1)
Last Admission Date: 11/24/01 (patient 108)
Recorded Parameters and Percentage of Patients Covered by Measurement

CIbi	HR	MAP	SapO2	tcO2/F	CiId	COrb 4.6	FIO2	PaO2 82.4	SaO2
99.1	100.0	100.0	100.0	100.0	46.3		100.0		82.4

SvO2	HCT	DO2I	VO2I	Qs/Qt	BE	L(mean)	R(mean)	L/R(mean)1	PtcCO2
49.1	83.3	50.0	50.9	50.0	80.6	17.6	17.6	7.6	100.0

Study Name: Pentaspan
Focus: Comparison of invasive and non-invasive measurements on a periodic basis.
Number of Patients: 64, 13 non-survivors, 10 no data on survival (available in other databases)
Earliest Admission Date: 11/26/01 (patient 1)
Last Admission Date: 4/13/02 (patient 64)
Recorded Parameters and Percentage of Patients Covered by Measurement

CIbi 100	HR 100	MAP 100	SapO2 98.4	PtcCO2 92.2	CItd 43.8	FIO2 100	PaO2 78.1	SaO2 78.1
SvO2 46.9	HCT 79.7	DO2I 45.3	VO2I 43.8	Qs/Qt 43.8	BE 76.6			

Table 2. Summary of WCS Physiological Parameters Versus Data Set and the Percentage of Patients Covered by Each Measurement

Parameter	**Fluid Resuscit. Protocol** 07/96 - 03/99	**Heart Rate Variability Protocol** 08/99 - 10/00	**Surgical ICU 2** 08/00 - 05/01	**Surgical ICU 3** 03/01 - 11/01	**Pentaspan** 11/01 - 04/02
CItd	25.2	56.4	67.2	46.3	43.8
CIbi	95.8	91.1	98.5	99.1	100.0
HR	95.8	96.6	100.0	100.0	100.0
MAP	94.3	96.6	100.0	100.0	100.0
SapO2	94.0	96.6	98.5	100.0	98.4
PtcO2	92.8	91.6	92.5	100.0	
PtcCO2	92.8	91.6	92.5	100.0	92.2
FIO2	94.9	96.6	100.0	100.0	100.0
SaO2	59.2	77.7	76.1	82.4	78.1
SvO2	16.5	46.4	52.2	49.1	46.9
HCT	60.7	77.7	76.6	83.3	79.7
DO2I	59.5	49.2	55.2	50.0	45.3
VO2I	16.5	45.3	52.2	50.9	43.8
tcO2/F	92.8	91.6	100.0	100.0	
PaO2		77.7	76.1	82.4	78.1
Qs/Qt		43.0	52.2	50.0	43.8
BE			56.7	80.6	76.6
COrb		20.7	25.4	4.6	
STAR		20.7	25.4		
CObi		91.1	98.5		
L(mean)		97.8	11.9	17.6	
R(mean)		98.9	11.9	17.6	
L/R(mean)		99.4	11.9	17.6	
HR(mean)		100.0	4.5		
VCO2			25.4		
ETCO2			25.4		
Pox			25.4		
TV			55.2		
RR			40.3		
Zo			3.0		
dZdT			4.5		
PEEP			50.7		
CVP			38.8		

Table 3. Listing of Medications, Blood Component Therapies, Resuscitation Fluids, and Procedures in the W. C. Shoemaker Data Sets

Medications	Blood Component Therapies and Resuscitation Fluids	Procedures
DOP (Dopamine)	RBC (Packed Red Blood Cells)	Intubation
DOB (Dobutamine)	Plates (Platelets)	Entubation
Morphine	Cryo (Cryoprecipitated Anti-hemophilic Factor)	Dialysis
NaHCO3	WBC (White Blood Cells)	Surgery (start/closing/end times)
Nitroprusside	**Colloids**	CPR
T4 (Thyroxine)	FFP (Fresh Frozen Plasma)	CT
Nitroglycerin	5%/25% Albumin	X-Ray
Lasix	Hespan	Swan-Ganz Catheter Insertion
Atropine	**Crystalloids**	bagging for respirator
25% Mannitol	Normal Saline	Chest tube insertion
Pentobarbiturate	Lactated Ringer's Solution	Angio (Angiography)
		Suction

Table 4. Definitions of Physiological Parameters in the W. C. Shoemaker Data Sets

BE
- Base Excess
- Blood Gas Lab results
- (dimensionless, pH)

CIBI
- Cardiac Index Bio Impedance
- IQ machine
- l/min/m^2
- Integration is 12 beats

CITD
- Cardiac Index measured by Thermodilution
- Pulmonary Artery Catheter
- l /min / m^2
- 5 minutes measurement time

COBI
- Cardiac Output Bio Impedance
- IQ machine
- l/min
- Integration is 12 beats

COrb
- Cardiac Output measured by CO2 Rebreathing
- Non-Invasive Cardiac Output (NICO)
- l/min

COtd
- Cardiac Output measured by Thermodilution Swan-Ganz TD Catheter
- l/min
- ~ 5 minutes integration time

CVP
- Central Venous Pressure
- Central Venous Line – average pressure from central line
- mm Hg
- ~ 5 - 10 minutes integration time

DO2I
- Oxygen Delivery Index
- Calculated from non-invasive systems, ICU computer
- ml/minute/m^2
- 15 minutes measurement time

dZdt
- change in baseline
- IQ machine
- Ohms/sec
- 12 - 15 beat average

ETCO2
- End Tidal CO2
- NICO
- Torr
- ~ 1 minute integration time

FIO2
- Fractional Inspired Oxygen Concentration
- Respirator

- Fraction (1.00 = 100% 0.10 = 10%)
- Machine setting, not a measurement

HCT

- Hematocrit
- Lab
- %

HR

- Heart Rate
- Bedside EKG if no dZdt or Z0 present, otherwise IQ machine
- Beats / Minute
- 10 – 15 cardiac contractions averaged

HR_mean

- Heart Rate
- HRV machine

beats/min

- 15 minutes integration time

L_mean

- LFA (Low Frequency Area)
- HR spectrum 0.04 – 0.10 Hz
- HRV machine
- Hz
- 15 minutes integration time

LR_mean

- Ratio of L/R
- Unitless
- 15 minutes integration time

MAP

- Mean Arterial Pressure
- Bedside monitor, most use A-line, some use cuff (only a very few).
- Not indicated in data set which was used
- mm Hg
- 10 – 20 seconds integration time

PAO2

- Arterial Blood Gas O2 tension
- Lab result
- Torr

PAP

- Pulmonary Arterial Pressure
- PA Swan Ganz Catheter
- mm Hg
- ~ 5 - 10 minutes integration time

PEEP

- Positive End Expiratory Pressure
- Respirator
- mm Hg

Pox

- (SapO2 from NICO, compared with SapO2 from Colin)
- Pulse Oximetry
- NICO
- %
- 5 – 10 seconds integration time

PtcCO2

- Transcutaneous CO2 Tension
- Novametrics
- Torr
- 30 seconds integration time

PtcO2

- Transcutaneous Oxygen Tension
- Novametrics
- Torr
- 30 seconds integration time

Qs_Qt

- Physiological Shunt Pulmonary Venous Admixture
- amount of blood going through lungs w/o being oxygenated
- Calculated from Swan-Ganz
- %
- 15 minutes measurement time

R_mean

- HFA (High Frequency Area)
- HR spectral curve with a 0.10 Hz window around
- fundamental respiratory frequency
- HRV machine
- Hz
- 15 minutes integration time

RR

- Respiration Rate
- Respirator
- Breaths / Minute
- 30 – 60 seconds average

SAO2

- Saturation of Arterial Hemoglobin
- Lab result
- %

SAPO2

- Pulse Ox
- Finger Cuff
- %
- 5 – 10 seconds integration time

STAR

- Goodness of ETCO2 measurement

- NICO
- 1-5 stars

SVO2

- Saturation Venous Oxygen
- Lab Result
- %

TCO2/F

- Transcutaneous O2 / FIO2
- Calculated from TCO2/FIO2
- Torr
- 30 seconds integration time

TV

- Tidal Volume
- Respirator
- liters
- 30 – 60 seconds integration time

VO2I

- Oxygen Consumption Index
- Calculated from Swan-Ganz TD catheter, ICU computer
- ml/minute/m2
- 15 minutes measurement time

ZO

- Baseline Bioimpedance
- IQ machine
- Ohms
- 12 – 15 beat integration

2.3.4 Quality Control for WCS database

In principle, the construction of a large database is a simple matter, but in practice it is not. The reason for this is that errors and inconsistencies in the incoming data must be isolated and corrected. As the database becomes very large, this becomes a significant problem. The two databases that are most susceptible to keying errors are the TR and WCS database. The SICU data is less problematic because the data acquisition is highly automated, physician review is required for data sign off, and supervisory software is used to prevent erroneously keyed entries from being inserted into the database.

2.3.5 Trauma Registry Database

This is a relational database that was converted to Microsoft Excel prior to being supplied to the sponsor. See Table 5 below for the parameters available. Also see Appendices B.4 and B.5.

2.3.6 ICU Database

This is a relational database in Microsoft Excel. See Appendices B.6 and B.7.

Table 5. Data points from the Trauma Registry (not all patients have data in all fields)

Sex

Race

Decade of age (e.g., "50" for 56-year-old)

Field

Injury Date

Injury Time

Transferred to LACUSC? Y/N

Mechanism of Injury Description

Mechanism of Injury code

Blunt/Penetrating and location in body

Field GCS

Field Airway Type

Initial Vital Signs
- Time
- BP
- RR
- Assisted? Y/N
- HR
- Temp
- Weight

GCS

Emergency Room/OR/Hospital

ER entry time and date

Triage criteria

Trauma team activation level

Trauma team time called

Trauma team time arrived

Location after ER (operating room, ward, etc.)

Location after ER time and date

Operating room anesthesia start time

Operating room anesthesia stop time

Location after Operating room

Pregnant Y/N

Labs/X-ray
- C-Spine
- CT Head
- CXR
- Pelvis
- Ultra Sound
- CT Abdomen
- CT Spine
- Facial Series
- Other
- HCT
- ETOH Y/N
- Toxicology Serum Y/N
- Toxicology Urine Y/N

Procedure
- ETT/CRIC/Trach
- ED Thoracotomy
- DPL (Peritoneal Lavage)
- Chest Tube: Lt/Rt
- CPR Duration

IV Fluids
- Pre-hospital
- ED IV Fluids
- Blood Products
- Autotransfusion

Abbreviated Injury Scale (AIS)
- (1=Head, 2=Face, 3=Chest, 4=Abdomen, Pelvis, 5=Extremities, 6=External (e.g., skin))

Injury Severity Score (ISS)

Blood (Total blood/products received during hospital stay, including Emergency Department)

Hospital Discharge
- Discharge Date
- Discharge Time
- Hospital Length of Stay
- Prior Phase
- Lived/Died
- Organ Donation Y/N
- Discharge to location (i.e., home, morgue, skilled rehab)
- Comments (gives acuity)

Discharge Diagnoses

Complications (ARDS, pneumonia, etc.)

Cause of death code(s)

2.3.7 Main Project Database

The Main Project Database consists of 732 trauma patients collected from 1996-2002 as the WCS database, and additional data on these patients from the TR and the SICU databases. The patients studied were monitored with state-of-the-art noninvasive sensors as well as with invasive techniques and procedures. Overall, the Main Project Database is considered to be very high in quality because the diagnostic measurements are comprehensive, and the prevalence of non-survivors is high, which gives the database the power to predict outcome. The Main Project Database includes temporal records of medications, blood component therapies, resuscitation fluids, and procedures. In addition, the location of the patient in the hospital is provided as a function of time. The temporal point of reference in the Main Project Database is the time of admission to LAC+USC Medical Center.

Both the WCS and TR databases involve significant numbers of keyed entries without the benefit of a supervising program to prevent unintended characters/values from entering the database.

2.3.8 Outcome Prediction with the Main Project Database

The outcome prediction component of this project was initially believed to be of high priority. However, in response to the change in the initial Statement of Work, this will now be performed by the sponsor. In our Year I and II activities, we expended significant effort as described below for outcome prediction.

> "Many different data items can be extracted from the combined database. Figure 3 shows a plot of the average Cardiac Index (CI), Heart Rate (HR), Mean Arterial Pressure (MAP), percentage oxyhemoglobin saturation ($SapO_2$), and transcutaneous O_2 tension divided by fractional inspired oxygen concentration ($PtcO_2/FIO_2$) versus time after admission to the LAC+USCMC emergency department. Patients with head trauma are not included in the sample population. Standard deviations are estimated from the data used to calculate mean values; they represent the spread in the distribution of data values about the mean…. A good predictor yields a large separation between the parameter distribution functions of survivors and non-survivors. It is clear that $PtcO_2/FIO_2$ in itself is a fairly good predictor of outcome, particularly at the earliest times after the trauma victim enters the hospital. The large $PtcO_2/FIO_2$ standard deviation for non-survivors near 10 hours is caused by a low patient count at this time. Other parameters shown in Figure 3 are not good predictors because they fail to produce large separations in survivor/non-survivor distribution functions. …many outcome predictors are currently being assessed as part of a more generalized study. These include initial heart rate, initial MAP, lowest MAP, initial cardiac index, APACHE II score, predictions of discriminant analysis, probability analysis based on the "nearest neighbors" of a patient's "state vector," $PtcO_2/FIO_2$, and the combination of $PtcO_2/FIO_2$ and $PtcCO_2$. At present the stochastic "nearest neighbor" analysis appears to be the best technique for outcome prediction, whereas $PtcO_2/FIO_2$ has emerged as the best single parameter predictor.
>
> Our search for optimum predictors of survival/non-survival is centered on finding physiological parameters that yield the maximum possible separation in distribution functions of survivors and non-survivors. In this regard, one examines positive (non-survival) and negative (survival) predictability. To measure the effectiveness of the predictor, one uses indices such as sensitivity (number who are positive and test positive/number who are positive) and specificity (number who are both negative and test negative/number who are negative). Initially the quantity $S = [(1\text{-sensitivity})^2 + (1\text{- specificity})^2]$ is minimized to establish a nominal parameter threshold and two-sided tests are used to determine the most promising predictors. Subsequently, trade-offs between sensitivity and specificity are made to arrive at the optimum parameter threshold. This methodology is not unlike that employed to interpret laboratory tests or to diagnose disease with clinical data. In our case, sensitivity measures how well the physiological quantity identifies those

who do not survive, that is, how sensitive it is. If a test has a high sensitivity, it will pick up nearly everyone who does not survive. Specificity measures how well the test excludes those who survive, that is, how specific it is. If a test has a very high specificity, it won't misclassify many survivors as non-survivors. Typically, one analyzes curves of sensitivity versus (1-specificity) to establish an optimum cutoff value.

The disadvantage of the sensitivity and specificity parameters is that they do not assess the accuracy of the test in a clinically useful way. However, they do have the advantage that they are not affected by the proportion of the trauma victims that do not survive, which is called prevalence. The effect of lower prevalence is much as one would expect: the lower the number of non-survivors in the study, the more certain we can be that a negative test indicates survival of a trauma patient, and the less sure that a positive result really indicates that the trauma victim did not survive. In the current investigation, predictive uncertainty is reflected in the *t* value of the double-ended Student's *t* distribution and in the fitting errors of sensitivity and specificity obtained when the quantity *S* is minimized. Because the prevalence of non-survivors is high in our study (20-25%), the uncertainty of the predictions is relatively low.

Software has been written to automatically examine the predictive values of a large number of parameters. The predictor analysis involves least-squares fitting to minimize *S* and yields sensitivity and error in sensitivity, specificity and error in specificity, optimum parameter threshold, mean of parameter value in non-survivors, mean of parameter value in survivors, standard deviations for the non-survivor and survivor distribution functions, and the *t* value for the double ended Student's *t* Distribution. The main W. C. Shoemaker database consisting of 689 patients is used as a derivation data set to search for predictors. A separate validation data set is being developed to confirm the predictors. The derivation data set is always subject to bias because the same data used to derive a predictor is also used to test its effectiveness. Consequently, there is a large program emphasis on securing more patient case histories. This is evidenced by the 40% increase in total number of retrospective trauma patients processed during the current grant year."

3. Key Research Accomplishments

- After the original Statement of Work was changed, we built the Main Project Database from noninvasively monitored patients collected prior to and during the funding period.
- We cleaned, deidentified and packaged the Main Project Database with explanatory material.

3.1 Building the Main Project Database

We obtained IRB approval from both USC and the Army to add patients collected into the WCS database during Year I of this project (September 29, 2001 - September 28, 2002) to the already approved retrospective patients collected into the WCS database prior to September 29, 2001. This IRB approval added approximately 180 patients to our study. The final set of 732 patients covers the period 1996-2002.

We identified 732 unique patients in the WCS database (5 patients were used in two of the five substudies for a total of 737 records) and combined the five Excel spreadsheets into one spreadsheet with a single line of headers (see all the headers in Appendix B.2).

We then obtained the electronic data from the ICU database pertaining to these patients' ICU stay and their TR data from the Los Angeles County Department of Health Services. The ICU database was provided in a relational format in Excel. The TR data was provided in a relational format in DBF files and we converted it to Excel using purchased software (ABC Amber DBF Converter, www.processtext.com/abcdbf.html)

3.2 Packaging and Delivering the Main Project Database

3.2.1 Deidentification of the data

The link between all three databases we obtained is the "patient identification number," a seven-digit number assigned to each patient in the Emergency Room at LAC+USC Medical Center. The WCS database uses only the patient identification number. The ICU database and the TR both link the patient identification number to an internal number unique to each patient that acts as the master link for that patient's relational files.

To deidentify the Main Project Database, we arithmetically transformed the patient identification number in all three databases. (We left intact the ICU and TR internal numbers.) The transformed patient identification number is now called the "Study ID" and serves as the link between all three components of the Main Project Database (see Appendix B.1 for a graphic presentation).

After ensuring the Study ID existed in all appropriate files in all three databases, we deleted the original patient identification number, patient names and all address information. For patients aged 20 and older, we rounded their ages down to the decade of age (a 57-year-old is listed as 50). For patients younger than 20, we left their age intact.

3.2.2 Glossary and descriptive lexicon

To allow the sponsor to effectively utilize the provided data, we wrote a glossary of terms for each of the three databases. For the two relational databases, we provided a list of headers and the types of data available in each relational file. (See Appendices B.3, B.5 and B.6).

4. Reportable Outcomes

4.1 Publications

1. Shoemaker WC, Wo CCJ, Botnan A, Bayard DS, Jelliffe RW: Development of a hemodynamic database in severe trauma patients to define optimal goals and predict outcome. CBMS 2001: Proceedings of 14th IEEE Symposium on Computer-Based Medical Systems (IEEE Computer Society, 2001), pp. 231-236.
2. Bayard DS, Botnan A, Shoemaker WC, Jelliffe RW: Stochastic analysis of therapeutic modalities using a database of patient responses. CBMS 2001: Proceedings of 14th IEEE Symposium on Computer-Based Medical Systems (IEEE Computer Society, 2001), pp. 439-444.
3. Shoemaker, WC, Wo CCJ, Chan L, Ramicone E, et al: Outcome prediction of emergency patients by noninvasive hemodynamic monitoring. Chest 2001; 120:528-537
4. Olinski M, Shoemaker WC, Reis E, Kerstein M: Current controversies in shock and resuscitation. Surg Clin North America 2001; 81:1217-1252
5. Shoemaker WC: New approaches to trauma management using severity of illness and outcome prediction based on noninvasive hemodynamic monitoring. Surg Clin N Am 2002; 82:245-255
6. Kern J, Shoemaker WC: Meta-analysis of hemodynamic optimization in high risk patients. Crit Care Med 2002; 30:1686-1692
7. Fathizadeh P, Shoemaker WC, Wo CCJ, Colombo J: Autonomic activity in trauma patients based on variability of heart rate and respiratory rate. Crit Care Med 2002, 32(6):1300-1305, June 2004.

8. Shoemaker WC, Bayard DS, Botnen A, Wo CCJ, Gandhi A, Chien L, Lu K, Martin MJ, Chan LS, Demetriades D, Ahmadpour N, Jelliffe R. Mathematical program for outcome prediction and therapeutic support for trauma beginning within 1 hr of admission: A preliminary report. Crit Care Med 33(7):1499-1506, July 2005.

4.2 Presentations

1. Shoemaker WC: Noninvasive monitoring of high risk patients using a new stochastic analysis and control system. Auckland, New Zealand April 8, 2002.
2. Shoemaker WC: Noninvasive monitoring of high risk patients using a new stochastic analysis and control system. Christchurch, New Zealand. April 10, 2002.
3. Shoemaker WC: Noninvasive monitoring of high risk patients using a new stochastic analysis and control system. Wellington, New Zealand, April 12, 2002.
4. Shoemaker WC: Noninvasive monitoring of high risk trauma patients using a new outcome predictor, stochastic analysis and therapeutic decision support programs. Sacramento County Trauma Service, Roseland Hospital, Sacramento CA. May 30, 2002.
5. Shoemaker WC: Noninvasive monitoring of high risk patients using a new stochastic analysis and control system for outcome prediction and therapeutic decision support system. Frankfort, Germany, June 6, 2002.
6. Shoemaker WC: Outcome prediction and decision support program in high risk trauma and surgical patients using a new stochastic analysis with a control system and a therapeutic decision support program. Berlin University, Germany, June 10, 2002.
7. Shoemaker WC: Noninvasive hemodynamic monitoring of high risk patients using a new stochastic analysis for outcome prediction therapeutic decisions. Mexican Pediatric Society, International Conference, Mexico City, Mexico, June 20, 2002.
8. Djuth FT, Belzberg H, Shoemaker WC, Elder JH, Zhu J, Wo CCJ: An open trauma database for studying hemodynamics including blood Flow and tissue perfusion failure, ATACCC Meeting, St. Petersburg Beach, FL, September 9-13, 2002.
9. Belzberg H, Elder JH, Djuth FT, Oder D, Shoemaker WC: The developing of a Trauma Outcome Data Analysis (TODA) tool: answering old questions with new techniques: ATACCC Meeting, St. Petersburg Beach, FL, September 9-13, 2002.
10. Shoemaker WC, Belzberg H, Bayard DS, Wo CCJ, Botnen A, Djuth FT, Choi A, Jelliffe, RW: Noninvasive hemodynamic monitoring of trauma patients for outcome prediction and decision support by a stochastic control analysis and display, ATACCC Meeting, St. Petersburg Beach, FL, September 9-13, 2002.
11. Shoemaker W.C: Outcome prediction in high-risk patients using noninvasive monitoring and a new stochastic analysis. USC Pharmacology workshop, Sept 30 –Oct 2, 2002
12. Belzberg H, Oder D, Djuth F, Wo CCJ, Shoemaker WC. Integrating databases: Changing a camel back into a horse. Advanced Technology Applications for Combat Casualty Care conference, St. Petersburg Beach, Florida, August 16-18, 2004.

5. Conclusions

1. Continuous physiologic monitoring using noninvasive technology is feasible in the first hours after trauma.
2. Integration of data from various databases is possible but extremely difficult. Databases that are not designed to be combined with other databases for data mining require significant translation. A common lexicon (Rosetta stone) must be created to complete an overall picture of a patient who has data stored in different databases.

3. Adoption of a standard set of identifiers for elements of a database will be essential for future advancement of data mining capabilities. Bodies such as the Institute of Electrical and Electronics Engineers (IEEE) and the American Society for the Testing of Materials (ASTM) are working towards a standardized set of identifiers and formats. However, these remain outside the mainstream of medical equipment and medical records. HL-7 [Ref. 11] is not sufficiently implemented or adequately robust to support all the database needs, especially the demographic descriptors.

6. References

1. Dunham CM, Cowley RA, Gens DR, Ramzy AJ, Rodriguez A, Belzberg H, Wiles CE: Methodologic approach for a large functional trauma registry. MMJ 1989; 38:227-233
2. Shoemaker WC: Invasive and noninvasive hemodynamic monitoring of high-risk patients. Seminars in Anesthesia, Perioperative Medicine and Pain 1999; 18:63-70
3. Shoemaker, WC, Wo CCJ, Chan L, Ramicone E, et al: Outcome prediction of emergency patients by noninvasive hemodynamic monitoring. Chest 2001; 120:528-537
4. Fathizedeh P, Shoemaker WC, Wo CCJ, Colombo J: Autonomic activity in trauma patients based on variability of heart rate and respiratory rate. Crit Care Med 2002, Submitted
5. Olinski M, Shoemaker WC, Reis E, Kerstein M: Current controversies in shock and resuscitation. Surg Clin North America 2001; 81:1217-1252
6. Kern J, Shoemaker WC: Meta-analysis of hemodynamic optimization in high risk patients. Crit Care Med 2002; 30:1686-1692
7. Shoemaker WC, Bayard DS, Wo CCJ, Botnan A, Chan L, Jelliffe RW, Djuth FT, Belzberg H: Noninvasive hemodynamic monitoring of emergency patients for outcome prediction by a stochastic control program. Submitted to Crit Care Med.
8. Shoemaker WC, Thangathurai D, Wo CCJ, Kuchta K, Canas, M, Sullivan MJ, Farlo J, Roffey P, Zellman V, Katz RL: Intraoperative evaluation of tissue perfusion in high-risk patients by invasive and noninvasive hemodynamic monitoring. Crit Care Med 1999; 27:2147-2299
9. Shoemaker WC, Belzberg H, Wo CCJ, Milzmann DP, et al: Multicenter study of noninvasive monitoring systems as alternatives to invasive monitoring of acutely ill emergency patients. Chest 1998; 114:1643-1652.
10. Temper KK, Shoemaker WC: Transcutaneous oxygen monitoring of critically ill adults with and without low flow shock. Crit Care Med 1981; 9:706-709
11. Dolin RH, Alschuler L, Boyer S, et al. HL7 clinical document architecture, release 2. JAMIA, October 12, 2005 (in press).

7. Appendices

Appendix A: Key communications with sponsor

Appendix B: Selections of final work product sent to the Army

Appendix C: Copies of seven publications listed in Section 4

Appendix D: List of study personnel

Appendix A

Communications relating to change in work plan

A.1 June 5, 2002 from Contract Reporting Officer, Dr. Jaques Reifman
A.2 August 12, 2002 from Dr. Reifman
A.3 August 30, 2002 from Dr. Belzberg to Dr. Reifman
A.4 October 25, 2002 from Dr. Reifman

Communications between Investigators and US Army Human Protection Specialist Showing Delays relating to adding data collected after September 2001

A.5 October 22, 2002 from Maryann F. Pranulis, RN, DNSc, Human Subjects Protection Scientist, US Army
A.6 April 7, 2003 from Dr. Pranulis
A.7a-d Our communications with USC HSC IRB 2002-2003
A.8 September 8, 2003 from Dr. Pranulis (re HSC IRB approval to add data 9/01-9/02)

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A.1

Subject: Summary of 4 June meeting
Date: Wed, 5 Jun 2002 15:21:28 -0400
Thread-Topic: Responses to your comments attached
From: "Dr. Jaques Reifman" <reifman@tatrc.org>
To: "howard belzberg" <belzberg@usc.edu>, <djuth@ix.netcom.com>
Cc: <doder@hsc.usc.edu>, "Dr. Jaques Reifman" <reifman@tatrc.org>

Howard & Frank,

Thanks for taking the time to meet with me yesterday. It was a good meeting, as always. Following please find a summary of the action items to be completed by the end of August in preparation for the ATACCC meeting in Sept. Please let me know if your recollection of yesterday's discussion differs from the summary below.
-Jaques

1. Will Shoemaker. Data dictionary needs to be developed for (new) Will Shoemaker database, with detailed description of values, devices used for measurements, integration times for measurements, biases in noninvasive versus invasive measurements, etc.

2. Howard Belzberg + Will Shoemaker. Comments column of Will Shoemaker (new) database needs to be transformed into 5 to 20 data columns containing pH, life saving interventions, patient transfer times between hospital areas (ED, Radiation, Surgery, etc.), etc.

3. Howard Belzberg. Determine 50-60 trauma registry items to be excluded from the database (irrelevant data, confidential data, etc.).

4. Frank Djuth. Integrate items 1-3 above into a single database.

5. Will Shoemaker + Frank Djuth. Breakdown a few questions suggested for data mining into 15 to 20 lines of query. Probe database and arrive at conclusions.

6. Conference call with Jaques Reifman by late July 2002 to determine whether Jaques can use his algorithms to extract patterns from the data set.

Jaques Reifman, Ph.D.

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USAMRMC/TATRC
504 Scott Street
Fort Detrick, MD 21702-5012
Voice: 301-619-7915
E-mail: reifman@tatrc.org

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A.2

Date: Mon, 12 Aug 2002 17:48:25 -0400
From: "Reifman, Jaques PHD" <reifman@tatrc.org>
Subject: RE: Technical Progress
To: howard belzberg <belzberg@usc.edu>, djuth@ix.netcom.com
Cc: doder@hsc.usc.edu, "Reifman, Jaques PHD" <reifman@tatrc.org>
Thread-topic: Responses to your comments attached

Howard & Frank,

We need to have a detailed Statement of Work (SOW), including major deliverables, deliverable dates and milestones, describing research to be performed next year in order to move forward with year-two funding. The SOW does not need to be long (about 3 pages or so) but needs to clearly describe the major milestones and associated time lines. Please provide a draft no later than 30 August 2002 so that we can incorporate it into the original SOW and avoid funding gaps. I am available to discuss next year's SOW at your convenience. Also, I am concerned about the lack of technical progress in the project. In Year 1, we should have completed a full database--integrating both Dr. Shoemaker as well as the ICU database--and developed new procedures to allow future trauma cased to be seamlessly added to the database. It seems that we will fall short of this original goal. Hopefully, we can catch up over the next 45-days and in year 2. Thanks.

-Jaques

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A.3

Date: August 30, 2002
To: Jaques Reifman
From: Howard Belzberg
Re: Status and plans for project. Potential roadblocks and new possibilities

Status
At present, the data has been integrated from three sources into the master database. The database has been designed and we have begun populating it with real patients. In particular, we have identified strengths and weaknesses of each of the sources of data. For example, Dr. Shoemaker's database contained much textual reference, which had to be converted to addressable data requiring much time and effort. The Trauma Registry database contained much extraneous data, which had to be identified and removed. The SICU database is huge, and required very careful translation from its proprietary tables to more general Sybase/Matlab-friendly tables.

After combining our various databases, we extracted 50 patients who had electronic records across all the databases into a "toy database." Several queries have been written and are in various stages of completion.

For example, our clinical investigators hypothesized that transcutaneous oxygen measurements would predict development of respiratory failure. Using research, clinical and registry databases, 40 patients with respiratory failure were matched (on severity of injury) with 40 patients without respiratory failure. Their transcutaneous oxygen ratios on admission were compared. The difference in the ratios was statistically significant ($P<0.0001$). This demonstrates that predictors of poor outcome can be identified using queries.

Three abstracts have been submitted to ATACCC.

Plans
We will enhance our patient data collection by expanding our noninvasive monitoring to earlier phases of the traumatic event. We will be using data acquired immediately on arrival in the hospital 24 hours a day, 7 days a week. We will focus additional data collection on early analysis of queries that have been performed on our existing database. For example, we will monitor transcutaneous oxygen saturation and inspired oxygen levels more frequently to test and confirm hypotheses generated by our queries.

We will develop documentation for the use and maintenance of the combined database. In addition, we will develop a user-friendly instructional tool to allow other users to include patients and perform queries.

We hope within the next year to be able to perform real-time testing of stochastic prediction of patient response to disease and therapy.

We will soon provide a structured process for managing data acquisition, query management, database refinement and user documentation.

Roadblocks

The major anticipated roadblock is complying with consent issues of Title 10. Implementation of a randomized prospective study will require both local IRB and federal IRB approval. It is becoming progressively more difficult to perform human studies on patients who are unable to grant informed consent.

Electronic integration of currently used sensors is progressing but remains incomplete. The acquisition of data from the bioimpedence cardiac output with the transcutaneous oxygen sensor remains a makeshift interface. Gaining cooperation between manufacturers to integrate these and other sensors remains a challenge. Alternatively, we will have to develop internally the capability to more seamlessly integrate these data sources.

New possibilities
We continue to be receptive to additional sensors for increasing the available data. In addition, we anticipate refining our data sets based on results of queries and observations of patient phenomena

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A.4

Date: Fri, 25 Oct 2002 17:32:25 -0400
From: "Reifman, Jaques PHD" <reifman@tatrc.org>
Subject: RE: Studies of Tissue Perfusion... Prop # 00089002,
Award #DAMD17-01-2-0070, HSRRB# A-10847
To: maryann.pranulis@det.amedd.army.mil
Cc: belzberg@hsc.usc.edu, "Reifman, Jaques PHD" <reifman@tatrc.org>
Importance: high
Priority: Urgent

Dr. Pranulis,

This is to recap our conversations and provide guidance to what is needed from Dr. Belzberg, as far as compliance to the USAMRMC IRB is concerned. Dr. Belzberg needs to prepare a protocol, to be amended to the original proposal, addressing the issues of concatenating de-identified patient data into a database and the analysis of retrospective, secondary patient data. All data used need to be patient de-identified and the patient needs to have been discharged from the hospital for the data to be included in the study. This should allow for use of future, to be collected patient data as long as these two conditions are met (in addition to the fact that no change of medical care takes place and no additional parameters are collected). I appreciate your willingness to guide Dr. Belzberg in this process and to review his protocol in an expeditious fashion, once the protocol is submitted to you with the adequate information. My understanding is that, given the special circumstances of this case, you might the able to turn it around and approve the protocol in a very short period, say, less than 30 days, once it has been properly submitted to you.

-Jaques Reifman

Jaques Reifman, Ph.D.
Senior Research Scientist
Director, Bioninformatics
USAMRMC/TATRC
504 Scott Street

Fort Detrick, MD 21702-5012
Voice: 301-619-7915
E-mail: reifman@tatrc.org

-----Original Message-----
From: Reifman, Jaques Dr TATRC [mailto:jaques.reifman@us.army.mil]
Sent: Thursday, October 24, 2002 5:49 PM
To: Reifman, Jaques PHD
Subject: FW: Studies of Tissue Perfusion... Prop # 00089002, Award #DAMD17-01-2-0070, HSRRB# A-10847
Importance: High

From: Pranulis, Maryann F Dr AMDEX
Sent: Thursday, October 24, 2002 5:48:38 PM
To: 'belzberg@hsc.usc.edu'
Cc: Reifman, Jaques Dr TATRC; Stotler, Karen S Ms USAMRAA; Duchesneau, Caryn L Ms USAMRMC; Pranulis, Maryann F Dr AMDEX

Subject: Studies of Tissue Perfusion... Prop # 00089002, Award #DAMD17-01-2-0070, HSRRB# A-10847
Importance: High

Dr. Belzberg:

Attached is a copy of your proposal with my comments, questions that need to be addressed, and suggestions inserted as tracked edits. I am also attaching a copy of our guidelines for protocol development for your reference. When you submit the protocol, please include a cover letter/memo requesting review of an amended protocol with a request for waiver of written consent. If you have questions about how to proceed, please contact me.

Best wishes,
Maryann F. Pranulis, RN, DNSc
Human Subjects Protection Scientist
AMDEX
maryann.pranulis@det.amedd.army.mil
(301) 619-6240
FAX (301) 619-7803
<<A-10847 baafinalsubmission (rec'd 23 Oct 02 -mfp edits).doc>> <<TEMPLATE - Protocol Guidelines (summarized from App J).doc>>

-=-=-=-=

A.5

Date: Tue, 22 Oct 2002 11:08:07 -0400
From: "Pranulis, Maryann F Dr AMDEX" <Maryann.Pranulis@DET.AMEDD.ARMY.MIL>

Subject: Seeking clarification about DoD study
To: "'belzberg@hsc.usc.edu'" <belzberg@hsc.usc.edu>
Cc: "Reifman, Jaques Dr TATRC" <jaques.reifman@us.army.mil>,
"Duchesneau, Caryn L Ms USAMRMC" <Caryn.Duchesneau@DET.AMEDD.ARMY.MIL>,
"Pranulis, Maryann F Dr AMDEX" <Maryann.Pranulis@DET.AMEDD.ARMY.MIL>
Importance: high

SUBJECT: Seeking clarification about the intent for continuation of the work on the protocol entitled, "Studies of Tissue Perfusion Failure at LAC & USCMC and the Incorporation of the Results into a National Trauma Database," submitted by Howard Belzberg, MD, Los Angeles County & University of Southern California Medical Center, HSRRB Log No. A-10847.0, Proposal No. 00089002, Award No. DAMD17-01-2-0070.

Dr. Belzberg,

From my telephone discussion with you on October 2nd and from my subsequent discussions with Dr. Reifman at TATRC, I am confused about the current status of your work and your intent for further work under the approved-as-exempt retrospective protocol and am seeking clarification.

When you said you no longer needed to do prospective data collection because you had more data than you expected from the retrospective study, did you mean that there were more medical records for the period of time (prior to 29 Sep 01) that you were approved for?

Or do you want to include medical records that were obtained after 29 Sep 01 until the present?

Please respond (by response email) as soon as possible. Your answer will affect the recommendations that HSRRB and Dr. Reifman make for the next step in the process for restoration of funding under this award.

Thank you for your prompt attention to this request.

Maryann F. Pranulis, RN, DNSc
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A.6

Date: Mon, 07 Apr 2003 10:27:45 -0400
From: "Pranulis, Maryann F Dr AMDEX" <Maryann.Pranulis@DET.AMEDD.ARMY.MIL>
Subject: A-10847.0 & A-10847.1 HSRRB review
To: "'belzberg@hsc.usc.edu'" <belzberg@hsc.usc.edu>,
"'djuth@ix.netcom.com'" <djuth@ix.netcom.com>
Cc: "Vandre, Robert H COL USAMRMC" <Robert.Vandre@DET.AMEDD.ARMY.MIL>,
"Reifman, Jaques Dr TATRC" <jaques.reifman@us.army.mil>,
"Stotler, Karen S Ms USAMRAA" <Karen.Stotler@DET.AMEDD.ARMY.MIL>,
"Brosch, Laura R LTC USAMRMC" <Laura.Brosch@DET.AMEDD.ARMY.MIL>,

"Duchesneau, Caryn L Ms USAMRMC" <Caryn.Duchesneau@DET.AMEDD.ARMY.MIL>,
"Pranulis, Maryann F Dr AMDEX" <Maryann.Pranulis@DET.AMEDD.ARMY.MIL>,
"Bennett, Jodi Ms USAMRMC" <Jodi.Bennett@DET.AMEDD.ARMY.MIL>

SUBJECT: Proposal and Protocol Entitled, "Studies of Tissue Perfusion Failure at LAC & USCMC and the Incorporation of the Results into a National Trauma Database," Submitted by Howard Belzberg, MD, Los Angeles County and University of Southern California Medical Center, Los Angeles, CA, Proposal No.00089002, Award No. DAMD17-01-2-0070, HSRRB Log Nos. A-10847.0 and A-10847.1.

Dr. Belzberg and Dr. Djuth,

1. The review of your revised proposal and the protocol for the "retrospective" analysis of existing electronic medical information has been completed and discussed with the Acting Chair of the Human Subjects Research Review Board (HSRRB). This amended proposal and new protocol have been tentatively approved (with restrictions); full HSRRB approval is pending documentation of the USC IRB review and approval of the revised documents. The restrictions include:

a. The electronic medical record data that will be used will include data from patients that were treated for hemorrhagic trauma and discharged from LAC-USCMC prior to the end of March 2004 and are provided to the investigators no less than six months after hospital discharge;

b. A protocol and supporting documents for the establishment of a National trauma database should be submitted for HSRRB review and approval prior to initiating this work; and

c. A protocol and supporting documents should be submitted to HSRRB for review and approval prior to initiating any prospective studies under this award.

2. Although the USC IRB had initially approved of the retrospective component of your study as qualifying for "exempt" from review, they also explicitly stated that if any changes were made, the proposal/protocol would need to be resubmitted for their review. Even if this statement were not included in their exempt status approval, the regulations require investigators to submit proposed changes to the IRB for review and approval prior to initiating the change. When you submit these documents to the USC IRB, you are advised to call their attention to the change in your intent in relation to "prospectively" (until 2004) obtaining privileged medical information after patient discharge in order to conduct a "retrospective" analysis of existing data and that you are requesting a waiver of elements of informed consent. Please note that the previous decision of the USC IRB may be altered by the enactment (due 14 April) of the Health Insurance Portability and Privacy Act (HIPPA). At the HSRRB level, this study does not qualify for exempt status but, if the USC IRB concurs that it qualifies for waiver of consent under the organization's operationalization of the HIPPA regulations at LAC-USC, the HSRRB can considered this to be a minimal risk study with waiver of elements of consent.

3. In addition to submitting **documentation of the USC IRB review/approval of the current version of this study, please submit a copy of the LAC-USC policy (or memo of procedures) regarding who is considered a "covered entity" at this institution**.

4. As a reminder, you continue to be restricted from using any of the existing medical record data for patients that were admitted for treatment after September 2001, the HSRRB approval date for the retrospective component of your study. You will receive official notification from the USAMRAA office when you are approved for using these records.

5. If you have any questions or concerns, please contact me. I am available Monday through Friday, 8:00 to 16:30 (Eastern time).

With very best wishes,
Maryann F. Pranulis, RN, DNSc
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(301) 619-6240
FAX (301) 619-7803

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A.7a

May 16, 2003

Chair, IRB
LAC+USC Medical Center
1200 North State St., Trailer 25
Los Angeles, CA 90033

Re: 016-038 Studies of Tissue Perfusion Failure at LAC+USCMC and the Incorporation of the Results into a National Trauma Database

Dear Chairman:

1. The retrospective portion of this proposal was initially approved on June 7, 2001. At the time, we told the IRB that we would be seeking approval in the future for a second phase of the project, which would involve real-time data-collection.

We have decided that this second phase will be the collection of noninvasively monitored data from trauma patients, in exactly the same manner as IRB# 967-015, “Noninvasive Monitoring of Acute Trauma Patients.” IRB# 967-015 is exempt and has a waiver of consent, because all data is collected by noninvasive means during the routine care of trauma patients.

In the current study, we are asking for IRB permission to use data that is collected subsequent to IRB approval and funding by the sponsoring agency (U.S. Army). However, we will not be accessing that data until 6-9 months after the patient is discharged. The data and the conduct of the study, therefore, will have no effect on patient care, and will be consistent with current HIPAA regulations.

The U.S. Army calls this kind of data collection “prospective,” which we feel is a confusing term. It is “prospective” in the sense that it occurs subsequent to IRB approval and funding. However, it is not “prospective” in a medical sense; it has no impact on patient care.

We are requesting exemption from review and waiver of consent for this second phase of the project.

2. As a second item, we are asking for authorization to integrate previously acquired deidentified data, collected under IRB# 967-015, into this study’s database, for the period from the IRB approval for THIS study on June 7, 2001 to the present.

For your records, we are enclosing the Year 2 and 3 Statement of Work and the Annual Report to the funding agency.

Thank you,

Howard Belzberg, M.D.
Associate Director Trauma/Critical Care
Department of Surgery
LAC+USC Medical Center

Attachments: Year 2 and 3 Statement of Work (7 pages)
Annual report

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A.7b

June 11, 2003

Chair, IRB
LAC+USC Medical Center
1200 North State St., Trailer 25
Los Angeles, CA 90033

Re: Studies of Tissue Perfusion Failure at LAC+USCMC and the Incorporation of the Results into a National Trauma Database

Dear Chairman:

This study was previously approved by the IRB as #016-038 on June 7, 2001. However, as it was an exempt study it was sent to the archives, and the archive company could not find the file as of May 29, 2003. Therefore, because we have two minor changes to make to our data collection strategy, we are resubmitting the study. Two copies of the entire packet are attached.

Again, we are requesting waiver of consent and exemption from review.

History: The June 7, 2001, approval was for analysis of de-identified patient data (obtained electronically from the electronic medical record in the SICU) that had been collected *prior* to the IRB approval. At the time, we told the IRB that we would be seeking approval in the future for a second phase of the project, which would involve real-time data-collection.

We have decided that this second phase will *not* involve real-time data collection. It will consist of analysis of de-identified patient data in exactly the same manner as #016-038. However, as mentioned, we would like to specify *when* the data will be collected.

1. First, we are asking for authorization to use deidentified data, collected under IRB# 967-015, , for the period from June 7, 2001 to the present. IRB# 967-015, "Noninvasive Monitoring of Acute Trauma Patients" is exempt from review and has a waiver of consent, because all data is collected by noninvasive means during the routine care of trauma patients and de-identified before use in that study. The data is taken directly from the electronic medical record in the SICU and noninvasively collected data during the patients' resuscitative period.

2. We are also asking for permission to use data that will be collected in exactly the same manner and setting as (1) but *subsequent* to IRB approval and funding by the sponsoring agency (U.S. Army). We will not be accessing that data until 6-9 months after the patient is discharged.

The U.S. Army calls this kind of data collection "prospective," which we feel is a confusing term. It is "prospective" in the sense that it occurs subsequent to IRB approval and funding. However, it is not "prospective" in a medical sense; it has no impact on patient care.

The data and the conduct of the study will have no effect on patient care, and will be consistent with current HIPAA regulations.

Thank you,

Howard Belzberg, M.D.
Associate Director Trauma/Critical Care
Department of Surgery
LAC+USC Medical Center

Attachments: Section I
Section II
Budget
Lab Utilization Form
Checklist

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A.7c

July 22, 2003

Chair, IRB

LAC+USC Medical Center
1200 North State St., Trailer 25
Los Angeles, CA 90033

Re: #036-050 Studies of Tissue Perfusion Failure at LAC+USCMC and the Incorporation of the Results into a National Trauma Database

Dear Chair:

1. We appreciate expedited review.

2. **Attached** find our initial grant application. In regards to the continuation, the sponsor has told us they need our IRB approval first in order to continue the project. The project has not been modified except for the time periods in which the data is collected.

3. The data that will be analyzed in this study is abstracted from the routinely collected medical record. Before we access the data, it has been collected and stored in several different databases. These are: 1) the trauma registry; 2) the SICU electronic medical record; 3) the database collected under #967-015, which is an exempt study. Methods: these data are collected as part of the routine care of all critically ill trauma patients. Data sets: The data sets are laboratory and physiologic observations on trauma patients admitted to LAC+USC. The included data elements are **attached**. Characteristics: the data is sequential, routine physiologic and laboratory measurements that characterize the physiology of the response to trauma.

It should be noted that under HIPAA regulations, the principal investigator of this study, in his capacity as a member of the clinical team, is authorized to have access to the protected health information of all patients eligible for this study. All patients potentially eligible for this study are by definition under the care of the Trauma Division at LAC+USC Medical Center.

4. All data that is collected into the three sources (see #3) has patient name and PF#. Once the principal investigator (PI) determines that a patient has data in each of the three sources, the PI assigns a randomly generated unique identifier to that patient's data. Then, the PI downloads the data from the three sources for that patient into a secure computer and eliminates all data that may identify the patient (name, PF#, date of birth, dates of admission and discharge, demographic info, age except to the nearest decade). The only patients we will study in this protocol are those that have data from all three sources.

It should be noted that under HIPAA regulations, the principal investigator of this study, in his capacity as a member of the clinical team, is authorized to have access to the protected health information of all patients eligible for this study. All patients potentially eligible for this study are by definition under the care of the Trauma Division at LAC+USC Medical Center.

5.i) This research presents no more than minimal risk of harm to the subjects and involves no procedures for which written consent is normally required outside of the research context. We have clarified #14 of Section II (**attached)** to conform with the explanation in #4 above.

5.ii) The requirement for a limited waiver to review medical records information to assess potential eligibility is not applicable because the PI has authority to access protected information,

including medical records, on all potentially eligible patients. Nobody except the PI sees the data of study patients before that data has been de-identified by the PI.

(1)(a) The identifying elements have been erased by the PI before the study patient data is released to any other person.

(1)(b) Electronic erasure of identifiers will be accomplished using secure computer processes.

(1)(c) The PI assures the IRB that no protected health information will be reused or disclosed to any other person or entity.

(2) The patients included in this study are critically ill and are not able to provide consent. The alteration of their records of the elimination of identifiers is the only practical way to conduct this research.

(3) The protected health information will be used by the PI only to link the three data sets. Beyond that, all data will be completely and irreversibly de-identified.

Thank you,

Howard Belzberg, M.D.
Associate Director Trauma/Critical Care
Department of Surgery
LAC+USC Medical Center

Attachments: Original grant application
Data elements
Section II v.2, clean and marked-up

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A.7d

September 19, 2003

Chair, IRB
LAC+USC Medical Center
1200 North State St., Trailer 25
Los Angeles, CA 90033

Re: #036-050 Studies of Tissue Perfusion Failure at LAC+USCMC and the Incorporation of the Results into a National Trauma Database

Dear Chair:

The following is our response to the notes dated September 2, 2003:

1. We have revised Item #25 in Section II of the IRB application as requested (attached).

2. The waiver of HIPAA authorization was granted and approved in the letter dated 9/2/03..

3. Data collected under IRB Proposal #016-038 is stripped of personal identifiers before being saved and used as part of that study. Therefore, it will not have any personal identifiers when it is incorporated into this study.

4. We are aware that if new sensors are used, that will require IRB approval. At this time we do not plan to use new sensors in this protocol (036-050).

Thank you,

Howard Belzberg, M.D.
Associate Director Trauma/Critical Care
Department of Surgery
LAC+USC Medical Center

Attachments: Section II v.3, clean and marked-up

-=-=-=-=

A.8

Date: Mon, 08 Sep 2003 14:07:17 -0400
From: "Pranulis, Maryann F Dr AMDEX" <Maryann.Pranulis@DET.AMEDD.ARMY.MIL>
Subject: A-10847.0 and A-10847.1 - Fax rec'd
To: "'belzberg@usc.edu'" <belzberg@usc.edu>,
"'djuth@ix.netcom.com'" <djuth@ix.netcom.com>
Cc: "Vandre, Robert H COL USAMRMC" <Robert.Vandre@DET.AMEDD.ARMY.MIL>,
"Convertino, Victor USAISR-Ft Sam Houston"
<Victor.Convertino@CEN.AMEDD.ARMY.MIL>,
"Brosch, Laura R COL USAMRMC" <laura.brosch@us.army.mil>,
"Duchesneau, Caryn L Ms USAMRMC" <Caryn.Duchesneau@DET.AMEDD.ARMY.MIL>,
"Pranulis, Maryann F Dr AMDEX" <Maryann.Pranulis@DET.AMEDD.ARMY.MIL>

Dr. Belzberg,

It was good to talk with you today and to learn that the USC IRB has finally approved of the HSRRB required revisions and HIPAA revision for the protocol, "Studies of tissue perfusion failure at LAC & USCMC and the incorporation of the results into a national trauma database." Congratulations!!

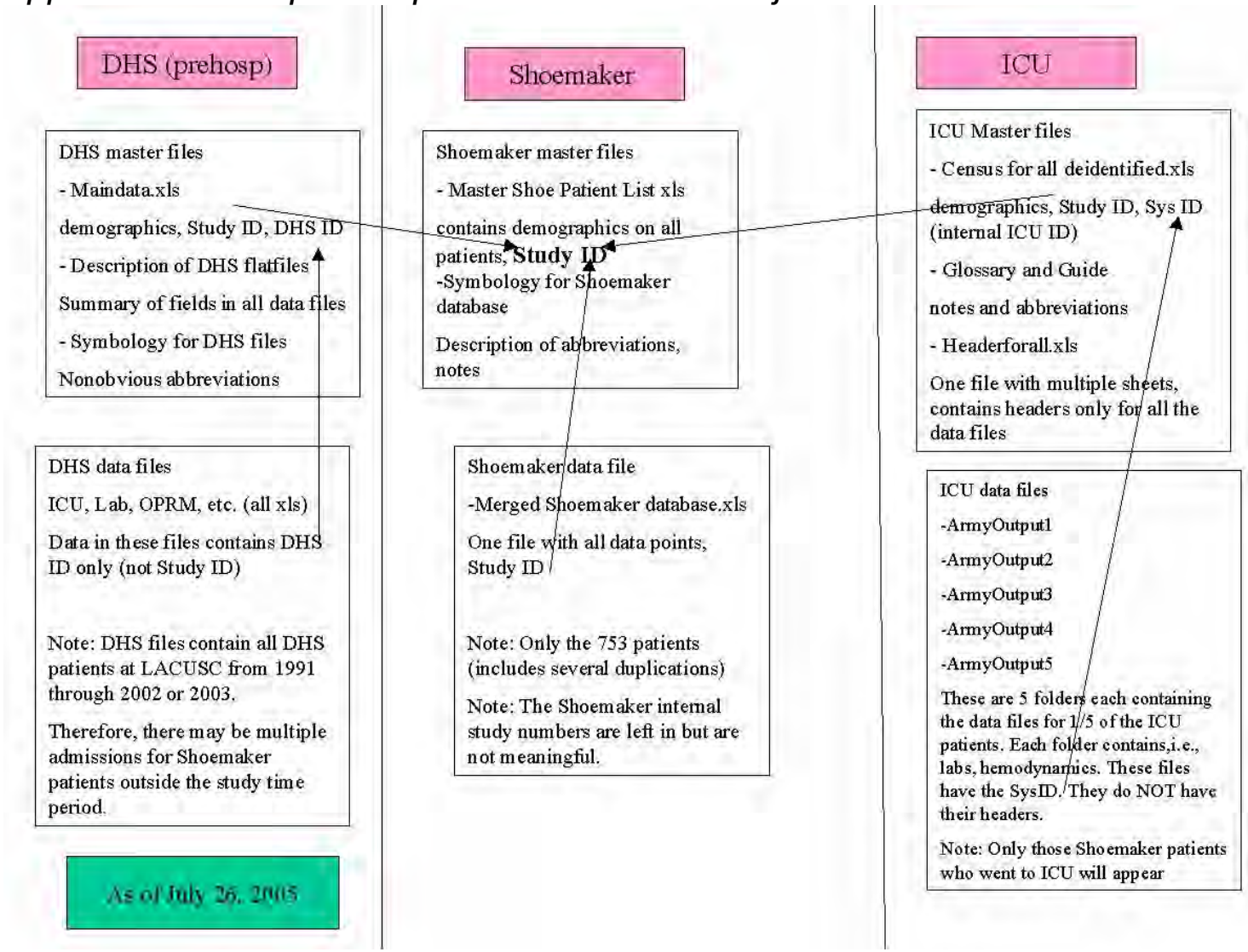
The faxed copy of the IRB approval was received this afternoon and is readable. I will complete processing the recommendation for HSRRB approval tomorrow and will notify you when the HSRRB approval memo is sent to the USAMRAA office. As a reminder, you are still restricted from re-starting this work until you receive official notification from the USAMRAA office that the restriction has been lifted.

Best wishes and please keep in mind that any changes will need HSRRB review and approval as well at the USC IRB's approval prior to implementation . Also, you will need to submit to the

HSRRB a copy of all of the documents you submit to the USC IRB for their continuing review (next spring) along with a copy of the IRB approval of continuation. If you have any questions or concerns about the human subjects aspects of this project, please contact me. I will continue to be your point of contact unless you are notified otherwise.

Maryann F. Pranulis, DNSc
Human Subjects Protection Scientist
AMDEX
maryann.pranulis@det.amedd.army.mil
(301) 619-6240
FAX (301) 619-7803

Appendix B.1 Graphic Depiction of the Main Project Database



Appendix B.3

GENERAL INFORMATION ABOUT THE SHOEMAKER DATABASE

July 20, 2005

Master Shoe Patient List .xls

This list file unifies the five Shoemaker studies:
Fluids Resuscitation Protocol 8/96 – 3/99
Heart Rate Variability 9/99-10/00
ICU2 10/00-4/01
ICU3 3/01-11/01
Pentaspan 11/01-4/02
NOTE: five patients had been double-counted in the HRV and ICU2 studies. I have marked the duplications on the list in yellow
NOTE: There is one patient who had two study admissions – his ID will show up twice and is marked in lilac.
NOTE: The five studies did not use exactly the same data fields. Because of the small number of patients, I have combined the demographics of all five studies into this one file. Some of the fields will be filled for one study and blank in another.
NOTE: Regarding AGE: for privacy purposes, all patients aged $\geq$ 20 have been rounded down to their decade of age. Anyone aged <20 are listed at their exact age. No birthdates should be appearing anywhere in these files.

NS/S field means Nonsurvivor/Survivor
BSA is body surface area in square meters. This is used to generate some of the data points in the Merged Shoemaker Databases file.

"Where" field

1202	Emergency Dept.
1350	Emergency Dept.
8700	8th floor ward
Angio	Angiography suite
BICU	Burns ICU
CMA	Step-down unit (lesser acuity SICU) This is the same as the Surgical StepDown listed in the ICU database
CT	CT
ICU	Surgical ICU (aka 9300)
OR	Operating room
PAR	Recovery room

Merged Shoemaker Databases.xls

This data file unifies the five Shoemaker studies:
Fluids Resuscitation Protocol 8/96 – 3/99
Heart Rate Variability 9/99-10/00
ICU2 10/00-4/01
ICU3 3/01-11/01
Pentaspan 11/01-4/02
NOTE: The five studies did not use exactly the same data fields. Because of the small number of patients, I have combined the data of all five studies into this one file. Some of the fields will be filled for one study and blank in another. See the headings for each study.
NOTE: I have kept the EVENT and NO fields (columns A&B) as these are internal to each study, and help you keep track of how many line entries each patient has.

Field symbology for this file

NS/S	Nonsurvivor/Survivor
PS	Probability of survival % (internally generated stochastic analysis real-time by the noninvasive monitoring system)
T	Time after admission in hours and fractions of hours
COtd	Cardiac output thermodilution, liters/min
COrb	Cardiac output by rebreathing, liters/min
VCO2	Volume of co2 production/minute, ml/min/m2 of body surface area
PCBF	Pulmonary capillary blood flow, ml/min/m2 of body surface area
ETCO2	End tidal CO2
Pox	Pulse oximetry %
STAR	Arbitrary reliability index (1-4, 4 is highest)
TV	Tidal volume, in ml/breath
RR	Respiratory rate, breaths/min
CObi	Cardiac output bioimpedence, ml/min/m2 of body surface area
CIbi	Cardiac index bioimpedence, ml/min/m2 of body surface area
Zo	Baseline impedence, ohms
dZdT	Derivative of Z score, changes in ohms per sec
HR	Heart rate, beats per minute
MAP	Mean arterial pressure
SapO2	Saturation of the arterial hct, %
PtcO2	Transcutaneous oxygen in torr
PtcCO2	Transcutaneous CO2 in torr
Citd	Cardiac index thermodilution, ml/min/m2 of body surface area
Cirb	Cardiac index by rebreathing, ml/min/m2 of body surface area
FIO2	Inspired oxygen, %
PtcO2/FIO2	Transcutaneous to inspired oxygen ratio
PaO2	Partial pressure oxygen, ml/100 ml
SaO2	Saturation of oxygen, %
Svo2	Saturation of venous oxygen, %
HCT	Hematocrit
DO2	Oxygen delivery, ml/min/m2 of body surface area
VO2	Oxygen consumption, ml/min/m2 of body surface area

Qs/Qt	Shunt, %
BE	Base excess, meq
PEEP	Positive end expiratory pressure, ml
CVP	Central venous pressure, cm of water
PAP	Pulmonary arterial pressure, mmHg
WP	Wedge pressure, mm Hg

Appendix C – Seven Publications

Critical Care Medicine
 Volume 32(6), June 2004, pp 1300-1305

Autonomic activity in trauma patients based on variability of heart rate and respiratory rate *

[Clinical Investigations]

Fathizadeh, Payman MD; Shoemaker, William C. MD; Wo, Charles C. J. BS; Colombo, Joseph PhD

From the Department of Surgery, Division of Trauma/Critical Care, Keck School of Medicine, University of Southern California, Los Angeles.

Supported, in part, by award DAMD 17-01-2-0070 by the U.S. Army Medical Research Acquisition Activity, Fort Detrick, MD. The content of the information does not necessarily reflect the position or the policy of the Government, and no official endorsement should be inferred.

Outline

Graphics

Abstract^

Objective: To evaluate the effects of sympathetic and parasympathetic nervous system activity on the heart rate and other hemodynamic variables in acute emergency patients with mild to moderately severe trauma.

Design: Clinical study.

Setting: Level 1 university-run trauma service.

Patients: Fourteen trauma patients studied immediately after admission to the emergency department.

Interventions: We measured heart rate and respiratory rate variability by spectral analysis in the early period of mildly to moderately injured patients and compared the patterns of the low- (Lfa) and high-frequency (Hfa) areas of variability.

Measurements and Main Results: The Lfa is the area under the spectral analysis curve within the frequency range of 0.04–0.10 Hz. This area reflects primarily the tone of the sympathetic nervous system as mediated by the cardiac nerve. The respiratory area or Hfa is a 0.12 Hz-wide frequency range centered around the fundamental respiratory frequency defined by the peak mode of the respiratory power spectrum. It is indicative of vagal outflow reflecting parasympathetic nervous system activity. The Lfa/Hfa, or "L/R ratio," reflects the balance between the sympathetic and parasympathetic nervous systems. The hemodynamic effects of bursts of autonomic activity in response to injury were explored by heart rate and respiratory rate variability measured with non-invasive hemodynamic monitoring consisting of bioimpedance cardiac output, heart rate, and mean arterial pressure to measure cardiac function and transcutaneous oxygen (PtcO2) to reflect tissue perfusion. During sudden surges of autonomic activity, we described increased heart rate variability reflecting increased Lfa and to a lesser degree to Hfa. Slightly later there was increased heart rate, mean arterial pressure, and cardiac index but decreased tissue perfusion indicated by the decreased PtcO2/Fio2 ratio.

Conclusions: Surges in autonomic activity in the period immediately after emergency department admission of trauma patients were associated with pronounced increases in cardiac index, mean arterial pressure, and heart rate and reduced tissue oxygenation.

The observation that heart rate and blood pressure vary from beat to beat was first made by Stephen Hales, who, in the 18th century, performed the first quantitative measurement of arterial blood pressure in the horse. He also observed correlation among respiratory cycle, beat-to-beat systolic pressure, and the intervals between beats. A quantitative, noninvasive means of autonomic monitoring based on heart rate (HR) and respiratory rate (RR) variability techniques provides a methodology for clinically evaluating autonomic nervous activity as a whole as well as the sympathetic and parasympathetic components (1–6). Sympathetic modifying drugs and clinical tests produce repeatable and sensitive changes in the low-frequency areas (Lfa) and the L/R ratio (which is the ratio between Lfa and high-frequency areas [Hfa]), suggesting that these variables reflect sympathetic nervous system (SNS) activity. Furthermore, parasympathetic modifying drugs and clinical tests produce repeatable and sensitive changes in the Hfa, suggesting that these Hfa values reflect parasympathetic nervous system (PSNS) activity (7–11).

Cardiac autonomic monitoring leads to earlier recognition of patients' physiologic status and may suggest timely, proactive therapy.

The autonomic nervous system (ANS) primarily acts to compensate for stress and acute illnesses, and these compensatory responses are reflected in acute hemodynamic reactions that can be monitored and measured quantitatively. Understanding of the role of the ANS-mediated neural input to the heart is needed to better understand hemodynamic responses to acute emergency conditions. However, because the ANS responds to various degrees and kinds of stress associated with acute trauma, the hemodynamic responses are not uniform but must be evaluated in their clinical context. Moreover, repeated ANS surges and their hemodynamic responses may vary greatly.

The present study uses noninvasive autonomic nervous system monitoring based on real-time HR variability technology in the initial period of patients recently admitted for blunt trauma. Early mild to moderate cases were selected because severe trauma cases particularly in the late stages had many associated extraneous and confounding influences that obscured underlying ANS function and the resultant hemodynamic patterns. The interacting components of the ANS were evaluated by spectral analysis of HR variability and RR variability to reflect the tone of the ANS (1–5). The clinical usefulness of these values is based on the concept that the normal SNS and PSNS work harmoniously to maintain homeostasis, which results in a stable power spectral content maintaining a balance of power as reflected by LFa and HFa.

In response to the long-standing recognition of beat-to-beat HR variations and their clinical relevance, Akselrod and colleagues (2–5) have explored the physiologic mechanisms that generate these fluctuations. Spectral analysis characterizes mathematically the physiologic mechanisms that generate variations in RR intervals. Spectral analysis calculates the frequency content of time-varying signals and offers a breakdown of the successive RR intervals into their frequency components (1–5).

The present study was designed to evaluate sympathetic (SNS) and parasympathetic (PSNS) activity in the very early stage of acute emergencies of mild to moderate severity. ANS responses of patients with severe life-threatening injuries have too many confounding and overwhelming influences to be satisfactorily evaluated using conventional statistics.

METHODS^

Clinical Series^

We studied 14 mild to moderately severely injured patients by noninvasive monitoring of autonomic nervous system activity within the first 1–4 hrs after admission to the emergency department before and during the initial fluid resuscitation, before radiologic diagnostic studies, and before the use of sedation, anesthesia, or vasoactive agents. There were two females and 12 males, mean age 33.9 yrs, ranging between 15 and 66 yrs of age. The mean injury severity score was 10.1 ± 4.8. The patients were not under the effect of anesthesia; three patients received mild sedation or one dose of pain medication. Fluid therapies were limited to intravenous infusions of crystalloids of <=100–500 mL before the HRV measurements. All of these study patients were discharged alive and well after 2–23 days of hospitalization. The demographic, salient clinical features, and medications are given in Table 1.

Table 1. Demographics, salient clinical features, and medications

Patients were selected based on the following criteria: hypotension (systolic blood pressure <100 mm Hg or mean arterial pressure <70 mm Hg), tachycardia (heart rate >100 beats/min), multiple long bone fractures, head injuries, or blunt abdominal and thoracic injuries. Exclusion criteria included arrhythmias, seizures, shivering, and delays in starting monitoring.

HR and RR Variability as Markers of Sympathetic and Parasympathetic Activities^

HR variability is defined as recurrent changes in beat-to-beat intervals, measured by RR intervals. Two skin electrodes placed on each side of the chest in the standard lead II electrocardiograph (ECG) configuration measure the instantaneous heart rate. The heartbeat intervals are recorded and the HR variability is plotted in the frequency domain to separate the high-frequency from the low-frequency components by spectral analysis. When HR variability is plotted in the time domain, it is difficult to distinguish the high-frequency components from the low, because the plotted curve reflects the sum total of all frequencies in that signal.

Variability in the instantaneous beat-to-beat heart rate intervals is a function of sympathetic and parasympathetic activity that regulates the cardiac functional response to the body's level of metabolic activity. The SNS primarily generates the low-frequency components of HR variability associated with more gradually increasing HR variability, because the sympathetic branch usually responds in 4 or 5 secs, which is slower than parasympathetic responses (12, 13). The PSNS primarily generates the high-frequency components and has sharper increases, since it typically responds in 1–2 secs (1, 12, 13).

In addition to analyzing the ECG signals, a respiratory signal is obtained by the same electrodes through impedance plethysmography estimated by chest expansion. Incorporating respiratory signal analysis enables one to independently measure each branch of the ANS. This provides the essential dimension missing from classic heart rate variability monitoring as it pertains to independent assessment of the ANS branches.

When the low-frequency, and high-frequency components were isolated within the HR variability spectrum, their respective areas under the frequency-domain HR curve were calculated as Lfa and Hfa. The Lfa and Hfa values were demonstrated to reflect sympathetic and parasympathetic tone, respectively, by independent digital measurements (2–5). The Lfa is computed as the area under the heart rate spectrum from 0.04 to 0.10 Hz. The Hfa, sometimes referred to as the respiratory frequency area (Rfa), is computed as the area within a 0.12-Hz wide portion of the heart rate spectrum centered around the fundamental respiratory frequency, which is defined by the peak mode of the respiratory power spectrum. The Hfa is indicative of the vagal outflow and reflects the PSNS influence on heart rate control. These measurements have been demonstrated to be reliable, repeatable, and specific for sympathetic and parasympathetic function (1–14).

Hemodynamic Monitoring^

Cardiac Output.^

An improved thoracic bio-electric impedance IQ device (Yantagh, Bristol, PA) was applied shortly after arrival in the emergency department. The noninvasive disposable prewired hydrogen electrodes were positioned on the skin, and three ECG leads were placed across the precordium and left shoulder (15, 16). A 100-kHz, 4-mA alternating current was passed through the patient's thorax by the outer pairs of electrodes, and the voltage was sensed by the inner pairs of electrodes; the voltage sensed by the inner electrodes captured the baseline impedance, the first derivative of the impedance waveform, and the ECG. The signal processing algorithm used a time-frequency distribution (modified Wigner distribution) analysis that increased signal-to-

noise ratios (15, 16). Previous studies have documented satisfactory correlations between thermodilution and bioimpedance cardiac output values for trauma patients in the emergency department, operating room, and intensive care unit (17–19). Limitations of the impedance cardiography are dysrhythmias, pulmonary edema, pleural effusion, hemothorax, excessive crystalloid infusions, and motion artifacts (14, 17–19).

Transcutaneous Oxygen Tension.^

We monitored transcutaneous oxygen tensions (PtcO2) using the Clark polarographic oxygen electrode during the observation period (19–26). The oxygen tensions were measured on the shoulder skin surface heated to 44°C to increase diffusion of oxygen across the stratum corneum and to avoid local skin vasoconstriction (24–25). Previous studies demonstrated the capacity of transcutaneous oxygen tensions to estimate skin oxygen tension as a reflection of tissue perfusion (19–26). PtcO2 was indexed to the Fio2 to give a PtcO2/Fio2 ratio because of marked PtcO2 changes produced by increased inspired oxygen. Limitations of the transcutaneous methods are that the thermal environment must be reasonably constant and the electrode must be changed to a nearby site and be recalibrated to avoid first-degree skin burns (19–29).

Experimental Design^

Continuous monitoring of HR variability with ANS-R1000 (Ansar, Philadelphia, PA) was started shortly after admission and before use of anesthesia or ionotropic agents and, when possible, before pain medication. HR variability was monitored continuously for 2–4 hrs in each patient to identify, record, and compare patterns of Lfa, Hfa, and L/R ratio with HR variability changes. We made an effort to exclude times when extraneous confounding events may have played a role by noting, recording, and eliminating from consideration the time periods of agitation, pain, cough, needle insertion, withdrawal of the needle from skin, local anesthesia, suturing of minor skin injuries, changes in position, dressing changes, talking, presence of friends and family members, the patient’s reaction to environmental sounds, need to urinate, and psychologically disturbing events. Periods when the patient was quiet and stable were considered in the present analysis.

Patterns of Lfa, Hfa, and L/R Ratio in Relation to Heart Rate Patterns^

Spectral analysis of HRV and RRV were automatically determined and displayed as continuous patterns of Lfa, Hfa, and L/R ratio in relation to simultaneous HR patterns. The continuous Lfa, Hfa, and L/R ratio were monitored within the format of consecutive 32-sec segments. Since observed changes occurred over varying lengths of time, we evaluated the sequential Lfa and Hfa patterns and HR pattern changes during prolonged time periods.

Sudden Marked Changes or Surges in ANS and Their Relation to Hemodynamic Values^

We compared changing patterns of Lfa, Hfa, and L/R during surges in ANS activity with simultaneous hemodynamic changes in mean arterial pressure, HR, cardiac index (CI), stroke index (SI), and PtcO2/Fio2 values during the initial postadmission period in the emergency department. Surges were defined as values >25 pbs (2). Inspection of the continuous ANS measurements revealed sudden bursts or surges of autonomic activity of widely varying magnitude that occurred in association with increases of heart rate. These surges are evaluated next.

RESULTS^

Changes in Lfa, Hfa, and L/R Ratio During Routine Continuous ANS Monitoring^

We studied 31.5 hrs of continuous second-by-second monitoring of Lfa, Hfa, and L/R ratio and compared them with simultaneous changes in CI, SI, HR, mean arterial pressure, and

PtcO2/Fio2. Figures 1 and 2 and Table 2 illustrate continuous simultaneous patterns of HR with Lfa, Hfa, and L/R ratios.

Table 2. Sudden increases (surges) in autonomic activity associated with simultaneous hemodynamic changes

Figure 1. Pattern of changes in heart rate (HR, upper fine line) plotted with corresponding changes in low-frequency areas (Lfa). bpm, beats per minute. Lfa is in pbs2.

Figure 2. Changes in heart rate (HR, upper curve) plotted with corresponding changes in six representative surges of low-frequency areas (Lfa, lower curve, heavy line). Note vertical dashed line represents the beginning of each Lfa surge; vertical dotted line represents the beginning of HR increases. The space between the arrows of the top horizontal line represents the duration of each Lfa surge. The space between the arrows of the second horizontal line represents the duration of the corresponding HR change. In each case, the beginning of the Lfa surge preceded the beginning of the HR change, and the peak of the Lfa surge preceded the maximum change in HR. bpm, beats per minute.

Relatively small changes in Lfa were associated with HR changes in the same direction in 86% of the monitored time (range, 81–92%, Fig. 1). Similarly, 66% of Hfa changes were associated with HR changes; this ranged between 55% and 86% in different patients. L/R ratio had the least relationship (61%) with HR variability patterns (Table 2).

The dynamic range of HR changes did not affect the sensitivity of HR pattern to Lfa and Hfa changes. That is, there were pronounced changes in HR with baseline ranges about 70 beats/min as well as in the tachycardia range of >100 beats/min. The range of changes in HR was roughly proportional to the simultaneous Lfa changes (Fig. 1).

Description of Sudden Surges in Lfa and Hfa^

The increase of Lfa and Hfa with sudden surges in ANS activity, defined by abrupt increases >25 pbs (2), occurred with significant increases in HR, CI, and mean arterial pressure (Fig. 2 and Table 2). There was a trend toward increased SI that did not achieve statistical significance. However, this indicated that the increased HR did not occur at the expense of reduced SI. Tissue perfusion reflected by PtcO2/Fio2 values decreased with surges of increased Lfa and Hfa values.

Relationship of Lfa Patterns to Heart Rate Changes^

The sudden surges in Lfa were associated with increased HR; the correlation coefficient between the baseline to peak changes was $r = .46$, the two-tailed $p < .08$. The low correlation may in part be due to the small numbers of responses as well as the widely disparate patterns that characterize regulatory responses and the marked differences in the clinical circumstances of the traumatic stress as perceived by the patients.

Temporal Relationship of Lfa and Heart Rate Changes^

The Lfa and the HR were simultaneously recorded so that temporal relationships could be more accurately determined. In each instance observed, the inflection point at the beginning of the Lfa rise and the peak of the Lfa increase preceded the comparable changes in the HR (Figs. 1 and 2). The mean difference between the inflection point marking the beginning of the Lfa increase to the comparable inflection point in the heart rate increase was 38.8 ± 6 secs.

Description of Sudden Lfa and Hfa Reductions^

Decreases in Lfa and Hfa occurred with significant reductions in CI, HR, and mean arterial pressure and with trends toward reduced Hfa and SI values (Table 3). PtcO2/Fio2 values tended to increase with reduced Lfa and Hfa values.

Table 3. Sudden decreases in autonomic activity associated with simultaneous hemodynamic changes

DISCUSSION^

Spectral analysis of heart rate and respiratory rate variability converts the heart and respiratory time domain signals to the frequency domain signals for analysis and calculation of the LFa and the HFa. The LFa is a measurement that includes information mostly from the sympathetics of the cardiac nerve, but there may be a parasympathetic influence from a few fibers from the vagus nerve, which carries the cardiac nerve (3–6). The LFa and the HFa provide insight into the cardiac sympathovagal balance (2) as well as the health and functioning of the ANS, both centrally and, to a lesser extent, peripherally (1, 12, 13).

The frequency of the peak mode of the respiratory spectrum is defined as the fundamental respiratory frequency, which is equivalent to the inverse of the respiratory rate at rest during normal breathing. The HR variability is affected by both SNS and PSNS activity. When the fundamental respiratory frequency is superimposed on the HR variability spectral frequency axis, the high-frequency PSNS component can then be isolated. The low-frequency SNS component is also isolated within the heart rate variability signal based on classic spectral analysis theory.

The clinical usefulness of spectral analysis of HR variability and RR variability is based on the hypothesis that ANS monitoring provides evidence that a particular level of treatment is adequate or insufficient. Noninvasive ANS monitoring provides this information as numerical trends in real time. The goal is to titrate intervention to the level that is most effective at that given time. Noninvasive monitoring of ANS by spectral analysis of HR and RR variability has been used in different studies of different health conditions such as sepsis (6), trauma and shock (14), depth of anesthesia (30–32), cardiac dysfunction (32–35), cardiopulmonary diseases (35), diabetic neuropathy (36–38), pain management, neonatal development as infant monitoring (39), pharmaceutical interactions (40), and brain death (14). In these studies, patients have been monitored for short periods of time to compare the average values of Lfa, Hfa, L/R ratio, and mean HR with values of normal populations. In the present study we collected Lfa and HR data on a simultaneous recording to evaluate more accurately their temporal relationships. It was not possible with our equipment to also collect other hemodynamic data on the same tracing. However, temporal changes in the other hemodynamic variables appeared to be comparable to that of the HR.

Invasive monitoring remains the most definitive means of evaluating circulatory function in high-risk patients, but it is costly, is personnel intensive, has complications, and is often started late in the course of illness after intensive care unit admission and the onset of organ failure. Delays in management of trauma patients have led to circulatory deficiencies, organ failures, and death. However, noninvasive monitoring techniques that are recently coming of age may reduce the risk and cost of invasive monitoring (14, 17–19). New noninvasive methodologies, such as ANS monitoring based on real-time HR variability, may also reduce delays in instituting therapy and thereby improve outcomes.

The increase in ANS activity beginning with the inflection point that starts the elevation of Lfa, as well as the peak in Lfa activity, precedes the comparable inflection points and peaks in HR.

Thus, ANS activity precedes increases in HR and is consistent with the concept that ANS activity initiates changes in HR and hemodynamic patterns.

As ANS monitoring becomes more widely used and as more is learned about the underlying mechanisms driving the ANS monitored variables, more descriptive hemodynamic correlations may be revealed (1–14).

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*See also p. 1420. [Context Link]

Key Words: heart rate variability; respiratory rate variability; estimation of autonomic nervous system activity; parasympathetic nervous system activity; sympathetic nervous system activity; blunt trauma; acute emergencies

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14th IEEE Symposium on Computer-Based Medical Systems (CMBS'01) p. 0231
Development of a Hemodynamic Database in Severe Trauma Patients to Define Optimal Goals and Predict Outcome
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Abstract
Abstract: Noninvasive hemodynamic monitoring systems provide continuously monitored on-line displays of data from emergency department admission to the OR, and to the ICU for early recognition of circulatory dysfunction in acute emergency conditions. The net cumulative deficits of cardiac index are estimated by thoracic electric bioimpedance, arterial hypoxemia is measured by pulse oximetry, and tissue perfusion is reflected by transcutaneous pO2. Based on a large database, survival was satisfactorily predicted by discriminant analysis and by a new stochastic analysis and control program.
Back to Top
Additional Information

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14th IEEE Symposium on Computer-Based Medical Systems (CMBS'01) p. 0439
Stochastic Analysis of Therapeutic Modalities Using a Database of Patient Responses
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Abstract
Abstract: This paper proposes a new method for stochastic analysis and control which does not require a model, but which is constructed directly from a raw database of patient responses to therapy. Roughly speaking, the basic idea is to evaluate a control (a therapeutic policy or modality) which has, on the average, proved to work well for similar patients in the database. By "similar" is meant patients who have the same covariates and who are in similar dynamical states. These concepts will be made more precise in the paper. The proposed stochastic analysis and control approach for databases is new, although it is motivated by methods of machine learning put forth in [1][2] and methods of dynamic programming for stochastic control given in [3][4].
Back to Top
Additional Information

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Mathematical program for outcome prediction and therapeutic support for trauma beginning within 1 hr of admission: A preliminary report *

[Clinical Investigations]

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Outline

Graphics

Abstract^

Objectives: The aims were a) to noninvasively monitor acute emergency trauma patients beginning within 1 hr after admission to the emergency department; b) to prospectively predict outcome; and c) to evaluate the relative effectiveness of various modes of therapy.

Design: Prospective outcome prediction study using a mathematical search and display model based on noninvasive hemodynamic monitoring.

Setting: A level I trauma service in a large university-run inner-city public hospital.

Patients: We studied 185 consecutively noninvasively monitored emergency patients.

Interventions: We noninvasively monitored cardiac index, mean arterial blood pressure, heart rate, pulse oximetry, and transcutaneous oxygen and carbon dioxide tensions beginning within 1-hr after emergency admission.

Measurements and Main Results: The cardiac index, pulse oximetry, transcutaneous oxygen tension, transcutaneous carbon dioxide tension, and mean arterial blood pressure were higher in survivors than in nonsurvivors in the initial resuscitation period and at the hemodynamic nadir. Heart rate and transcutaneous carbon dioxide tension were higher in the nonsurvivors. The calculated survival probability in the first hour observation period of survivors averaged 85 ± 14% vs. 69 ± 16% for nonsurvivors ($p = .0001$). Misclassifications of the series as a whole were 11.3%; after excluding brain death from severe head injury, there were 6.4% misclassifications. A decision support system evaluated the effects of various therapies based on responses of patients with similar clinical-hemodynamic states.

Conclusion: Noninvasive hemodynamic monitoring and an information system provided a feasible approach to predict outcome early and to evaluate prospectively the efficacy of various therapies.

In the resuscitation of acute emergency trauma patients, time is crucial because delays in correcting circulatory deficiencies lead to shock, organ failures, and death (1–10). When invasive monitoring was started late in the course of illness or after organ failures began, goal-directed therapy with invasive pulmonary arterial catheters did not improve outcome (11–18). However, early or preoperative hemodynamic optimization was reported to improve outcome in peripheral vascular surgery (19), trauma (20), cardiogenic shock (21, 22), and sepsis (23). Recently, Rivers et al. (24) in randomized control studies demonstrated improved survival of septic patients whose treatment was guided by noninvasive monitoring plus a central venous pressure catheter with an

attached oximeter in the emergency department (ED). Noninvasive hemodynamic monitoring combined with an information system that predicts outcome is presently available (25–27). The issues are analogous to early diagnosis and therapy for cancer, where earlier diagnosis allows more effective therapy. Acute injury was studied because, in contrast to the insidious development of many medical illnesses, severe injuries occur shortly before admission and the course of their circulatory events may be monitored from the time of admission until hemodynamic conditions become stable (8, 25, 26). Traditionally, invasive pulmonary artery catheters provide hemodynamic data needed to evaluate the circulatory status of critically ill patients. However, the disadvantage of the pulmonary artery catheters is that they require critical care conditions. By the time of intensive care unit (ICU) admission or after onset of an organ failure, it is late in the course of illness.

Recently, Bayard et al. (27–29) developed a mathematical method that used a large database of noninvasively monitored hemodynamic variables to provide on-line real-time displays, outcome prediction, and therapeutic decision support for newly admitted acute emergency patients. The present report applies this probability analysis to the initial resuscitation of severely injured patients beginning within 1 hr of ED admission and continued until the patient was stabilized.

MATERIALS AND METHODS^

Clinical Series.^

We studied 185 consecutively noninvasively monitored emergency patients with major blunt or penetrating injuries and significant risk of mortality or morbidity within 1-hr of ED admission. All severely traumatized patients who could be monitored were studied and none were excluded. There were 141 survivors and 44 patients who died during their current hospitalization; the mortality rate was 23.8%. Noninvasive hemodynamic monitoring was begun in the ED within 1 hr (mean 29 ± 21 mins), and the patients were followed to the radiology suite when indicated, to the operating room (OR), and then to the ICU. When clinically indicated, pulmonary artery catheters were inserted after the patient arrived in the ICU. The time of monitoring, time of operations, times of ICU admission, and hospital discharge or death were recorded relative to time elapsed after ED admission.

In addition, the following data were included in the database: age, gender, presence of sepsis, Glasgow Coma Score, Injury Severity Score, the primary bodily injuries, covariates, hemodynamic patterns by invasive and noninvasive methods, organ failures, other complications, hospital days, ICU days, and hospital outcome. The proposed computerized program is an information system that is not directly connected to the patient as a closed loop system. It is comparable to monitoring the vital signs and the provision of on-line real time displays of data and calculations to inform the attending without interfering with the attending’s responsibilities or capacities to render patient care. Table 1 lists the salient clinical features. The Institution’s Review Board approved the protocol.

Table 1. Clinical features of the series

Noninvasive Hemodynamic Monitoring.^

Hemodynamic values were evaluated by continuous online real-time display of noninvasive monitoring of cardiac, respiratory, and tissue perfusion functions. The data were downloaded every 30 secs, averaged over 5-min intervals, and entered into the database. When consistent hemodynamic patterns were demonstrated, the data were averaged over 15-min periods for presentation. The noninvasive hemodynamic monitoring was continued until the patients were stable.

Cardiac Output and Cardiac Index.^

A thoracic bioelectric impedance device (IQ 101, Noninvasive Medical Technologies LLC, Auburn Hills, MI) was applied shortly after arrival in the ED. The noninvasive, disposable, prewired hydrogel electrodes were positioned on the skin, and three electrocardiograph leads were placed on the precordium and each shoulder (25, 30, 31). A 100-kHz, 4-mA alternating current was passed through the patient's thorax by the outer pairs of electrodes and the voltage was sensed by the inner pairs of electrodes, which captured the baseline impedance, the first derivative of the impedance waveform, and the electrocardiograph. Previous studies have documented satisfactory correlations between thermodilution and bioimpedance cardiac output values for trauma patients in the ED, OR, and ICU (25, 26). Limitations of the impedance method include faulty electrode placement, motion artifacts, restlessness, shivering, pulmonary edema, pleural effusion, valvular heart disease, dysrhythmias, and electrical leaks from other instruments using the same circuit.

Pulse Oximetry.^

Routine pulse oximetry (Nellcor, Pleasanton, CA) was used to continuously assess arterial oxygen saturation (Sao2). Values were observed continuously and recorded along with cardiac index measurements. Sudden changes in these values were confirmed by standard blood gas analysis (25).

Transcutaneous Oxygen and Carbon Dioxide Tensions.^

Conventional transcutaneous oxygen tension measurements (Ptco2) were indexed to Fio2 (Ptco2/Fio2) and continuously monitored throughout the observation period. Ptco2 technology uses the Clark polarographic oxygen electrode routinely used in standard blood gas measurements (32–36). Ptco2 was measured on a thoracic skin surface heated to 44°C to increase diffusion of oxygen across the stratum corneum (33–36). The Severinghaus electrode was used to continually monitor transcutaneous Co2 tension (34). Limitations of the transcutaneous methods are that the thermal environment should be reasonably constant. Marked changes in room temperature from drafts or open windows should be avoided and the electrode changed to a nearby site and recalibrated at 4-hr intervals.

Mathematical Details: The Search and Display Program.^

Bayard et al. (27) developed a search and display (stochastic analysis) program to determine individual patients' survival probabilities (SP) from a database of patients with similar clinical-hemodynamic "states," defined by the primary diagnosis, covariates, and hemodynamic variables. By "similar" is meant a group of patients with the same diagnosis and covariates and with similar hemodynamic patterns to the newly admitted patient under study. These are referred to as "nearest neighbors." Mathematically, the stochastic analysis was motivated by methods of machine learning (37, 38) and methods of dynamic programming for stochastic control (28, 29).

The state vector, x(t), at time t is described in terms of the various hemodynamic measurements, their derivatives, and their integrals. Assume that there are L different types of measurements taken on a given patient (e.g., cardiac index, blood pressure, pulse oximetry, and transcutaneous oxygen and Co2 tensions). Specifically, for each measurement type, denoted as y1, define the state vector as a concatenation of the value y1 itself, its first and second derivatives y'1, y"1, and its first integral [integral]y1dt, as follows:

Equation (Uncited)

That is, for L different measurement types there will be 4L states. In practice, the derivatives and integrals are approximated by finite differences and sums of the time-ordered data of the database. Specifically, we will calculate the approximations (27):

Equation (Uncited)
Control Input Definition.^

The “control input” (mode of therapy) will be chosen from a finite set of control inputs that can be applied to the system.
System Dynamics.^

It is convenient to think of the propagation of the patient’s state xk at time tk to his state xk+1 at time tk+1 as obeying the following nonlinear dynamical system with process noise wk and variables p, that is:

For simplicity, p is discrete and is assumed to be drawn from a finite set formed by enumerating all useful combinations of clinical covariates,

Both the clinical covariates and process noise help to explain the variability of patient responses of the database. The covariates help to distinguish gross differences in responses of patients with major differences in the nature of their disorders. Process noise helps to explain small differences between patients with the same diagnosis and covariates but different responses to the same therapy. It is a measure of unmodeled dynamics, or intraindividual variability, from other sources of variability in the system (27).
Probability of Survival.^

A patient’s SP for a given state x is denoted by S(x), which is calculated by first extracting the 40 or more nearest neighbor states of patients having the same diagnosis and covariates as well as hemodynamic values that are closest to the given patient’s values. The SP is then calculated as the fraction of these nearest neighbors who survived. The prospectively determined predicted outcome of each patient was validated by the patient’s actual hospital outcome determined at the end of the study.
Therapeutic Decision Support Programs.^

The therapeutic decision support program uses a database of therapeutic responses to evaluate the relative efficacy of various therapies by the responses of the patient’s nearest neighbors. The prospectively estimated therapeutic responses of each patient’s nearest neighbors were validated by the patient’s actual response to each selected therapy.
Statistical Analyses.^

The survivors’ and nonsurvivors’ deficits of mean arterial pressure (MAP), cardiac output, Sao2, and transcutaneous oxygen were calculated for the periods of monitoring. For categorical variables, differences in proportions between survivors and nonsurvivors were tested using the chi-square test or the two-tailed Fisher’s exact test. For continuous variables, the equality of the means between survivors and nonsurvivors was tested by the two-sample Student’s t-test or the Wilcoxon two-sample test. The effects of time, outcome group, and their interaction on survival probability and on each hemodynamic variable were analyzed by the mixed linear model using residual maximum likelihood with the unstructured covariance. The SAS statistical software (SAS System, release 8.2, SAS Institute, Cary NC) was used.
RESULTS^

Hemodynamic and Survival Probability Values From the Time of Admission.^

Figure 1 illustrates an example of a patient monitored from the time of ED admission. Table 2 lists the mean values ± sd for survivors and nonsurvivors during the first hour after admission. Figure 2 illustrates the time course of survivors' and nonsurvivors' hemodynamic patterns during the first hour plus a second hour follow-up. Mean ± sd values are shown for cardiac index, heart rate, MAP, Sao2 by pulse oximetry, Ptco2/Fio2, and SP. The cardiac index, MAP, Sao2, Ptco2/Fio2, and SP values of the survivors were significantly higher than the corresponding values of those who died, whereas the heart rate and transcutaneous Co2 tension were initially higher in the nonsurvivors. During the first 12 hrs, the mean SP of survivors was 85 ± 14% and of nonsurvivors 69 ± 16% ($p < .0001$).

Figure 1. An illustrative example of data of a 66-yr-old man who sustained a motor vehicle accident with lacerations of the spleen and descending thoracic aorta, hemothorax, and multiple rib fractures. The Injury Severity Score was 59, the Glasgow Coma Score was 9, and he sustained blood loss >4000 mL. He was operated on between 1 and 5 hrs after ED admission for splenectomy and repair of the thoracic aortic laceration. He was given 7 L of lactated Ringer's solution, 8 units of packed red blood cells, and 1500 mL of starch in the operating room, and he was given 5 units of fresh frozen plasma in the intensive care unit postoperatively for continued bleeding. Despite evidence of hypovolemia, the operating attending surgeon was reluctant to give more fluids for fear of disrupting the repaired aortic laceration. The patient developed acute respiratory distress syndrome, sepsis, cardiac failure, and renal failure. He died 31 days after admission. CI, cardiac index; MAP, mean arterial pressure; Sapo2, arterial oxygen saturation.

Table 2. Survival probability and hemodynamic values for the first hour after admission

Figure 2. Survivors' (solid line) and nonsurvivors' (dashed line) temporal patterns are shown for the first hour after their emergency department (ED) admission with a second follow-up hour in 185 trauma patients. Mean values ± sem are shown for cardiac index (CI), heart rate (HR), and mean arterial pressure (MAP). All values are keyed to the time of ED admission. Note that the survivors' CI and MAP values were generally higher than those of the nonsurvivors.

Calculated Survival Probability Compared With Actual Outcome on Hospital Discharge.^

The survival probabilities in the 185 prospectively monitored patients calculated during the first 24 hrs were compared with the actual hospital outcome when the patient died or was discharged from the hospital several days or weeks later. The survivors' SP values averaged 85%; the nonsurvivors' SP values averaged 69%. Using 77%, which was the halfway point between survivors and nonsurvivors, as the cut point, there were 21 (11.3%) patients who were misclassified in the series as a whole (Table 3). Excluding brain death from severe head injury, which has a different circulatory pattern, there were 12 (6.4%) misclassifications.

Table 3. Summary of classifications (n = 185)

Receiver Operating Characteristic Curves.^

Figure 3 shows receiver operating characteristic curves calculated for all data collected over the first four hours. Table 4 shows the data of the receiver operating characteristic curve changes in the survival predictor together with the conventional monitored hemodynamic values, that is, cardiac index, MAP, heart rate, and transcutaneous oxygen tension over time. The SP data reflect the vital signs as well as other hemodynamic values in terms of their ability as markers of outcome.

Figure 3. Receiver operating characteristic (ROC) curves and calculated areas under the curve for representative variables: survival probability (0.88), transcutaneous oxygen tension/Fio2 ratio (0.74), mean arterial pressure (0.73), and cardiac index (0.68).

Table 4. Area under the receiver operating characteristic curves at various times
Initial Low Values and Early Deterioration in Survivors.^

Inspection of individual patients' hemodynamic patterns showed in 30 patients distinct episodes of circulatory deterioration shortly after ED admission that were obscured by the higher values of the whole series. However, when these episodes were oriented specifically in relationship of the SP nadir (Fig. 4, SP pattern in bottom plot) the pattern of events with sudden hemodynamic deterioration was seen. Before the time of the SP nadir, the mean cardiac index decreased to 3.5 L/min/m2, MAP decreased to 80 mm Hg, Sao2 decreased to 96%, and Ptco2/Fio2 decreased to <125 torr.

Figure 4. Sudden episodes of circulatory deterioration in survivors (solid line) and nonsurvivors (dashed line). The timing of the data was realigned before and after the nadir to show the sequence of changes unobscured by the higher values of the rest of the series. The pattern of changes suggests that earlier decreases and earlier recovery occur with cardiac index (CI), mean arterial pressure (MAP), and transcutaneous oxygen tension/Fio2 ratio. HR, heart rate; SapO2, arterial oxygen saturation.
Therapeutic Decision Support System.^

The mathematical analysis of hemodynamic patterns also was used for support of therapeutic decision making. This analysis was based on data observed to occur in very similar patients (i.e., the nearest neighbors) recorded in the database. Figure 5 illustrates a patient's nearest neighbors' responses to various therapeutic interventions measured in terms of the estimated survival probabilities before and after each intervention. The prospectively determined predicted outcome of each patient was validated by that patient's actual hospital outcome at the end of the study. Similarly, the prospectively determined therapeutic responses of each patient's nearest neighbors were validated by the actual responses. The data in Table 5 illustrate how the monitoring may be used and suggest that in the stable, resuscitated patient, there is not much difference in the responses to the choice of fluids. Single infusions of a fluid may not be expected to produce marked changes in the stable patient. This table was not meant to be relevant to the problem of massive volumes of either agent.

Figure 5. The upper half of the window, left side, shows data of patient 206, the calculated survival probability (Psurvive) (30%), and most recent therapy given. The next section has two columns of the current hemodynamic values: cardiac index (CI), heart rate (HR), mean arterial pressure (MAP), arterial oxygen saturation (SapO2), transcutaneous oxygen tension (Ptco2)/Fio2, transcutaneous carbon dioxide tension (PtcCO2), and hematocrit (Hct) value in the first column, and the net cumulative excess (+) or deficit (-) of each variable up to this point in time in the second column. In the lower half of the window, the first column shows the number of nearest neighbors (NN) given each therapy. The second column shows the average survival probability of these nearest neighbors (Ps-NN) before therapy was given. Column 3 shows the number of nearest neighbors who were given each of the specified therapies in columns 6 through 8. Column 4 shows the survival probability of these nearest neighbors after administration of the therapy specified in columns 6 through 8. RBC, red blood cells; ALB, albumin.

Table 5. Predicted survival probability (SP) before and after therapy

Table 5 summarizes the SP before and after various fluid therapies given for resuscitation in the first 2 hrs after ED admission. In the survivors there were moderately good responses to each class of therapy, but nonsurvivors had poorer responses with greater variability. The mean difference between the predicted SP change for selected therapies and the actual observed SP changes was 2.9%. This was considered less than the actual effects, because in many cases there were continuing blood losses that could not be easily quantified.

Misclassification Rates of Survival Based on Outcome Predictors.^

Single initial or lowest values for MAP, heart rate, and cardiac index, Acute Physiology and Chronic Health Evaluation II scores, and discriminant analysis were compared with the present program (Table 6). Misclassifications of survival based on isolated hemodynamic variables averaged between 15% and 49%. The misclassification based on SP was 11.3% in the series as a whole but only 6.4% when patients without severe head injury and brain death were excluded. Brain death has a very different hemodynamic pattern because central vasoconstriction has been obtunded.

Table 6. Misclassifications in outcome prediction by selected variables

DISCUSSION^

The proposed analysis of the clinical-circulatory status in acutely ill patients defines the patient's state by diagnostic categories, clinical covariates, hemodynamic variables, their trajectories' first and second derivatives, and integrals. The accuracy and reliability of this approach depend on the size and comparability of the database that is needed to provide an adequate group of nearest neighbors. The present database contains >800 high-risk trauma patients with >36,000 time lines of data, each of which represents a patient's clinical-hemodynamic state. This database was found to provide adequate numbers of clinical-hemodynamic states to select nearest neighbors for this study. The mean difference between the patients' and nearest neighbors' values was 0.3 sd. Although the average SP in survivors does not appear to improve very much in time, it should not be expected to, particularly after the patients are stable and fully resuscitated. After a patient achieves 85% survival, small changes are not as important as the marked changes during initial resuscitation. As illustrated in Figure 1, the SP may vary widely during initial resuscitation or in the OR and cross the survival-nonsurvival line many times.

The problem of evaluating small changes from the figures, which show mean values of the series, may be due to the fact that only a small minority of patients suddenly deteriorate hemodynamically at any given time. When only a few patients suddenly deteriorate, their changes are obscured by other patients who are not changing at that time. This phenomenon is addressed and illustrated in Figure 4, where all the early sudden deteriorations were realigned in time before and after the SP nadir. In this part of the study, the cardiac index, MAP, Sao2, and Ptco2/Fio2 in both survivors and nonsurvivors tended to rise and fall, in general, with the rise and fall of the SP. The SP decreased from 90% to 72% in survivors and from 69% to 46% in the nonsurvivors.

The approach presented here is similar to that of experienced clinicians who can recall similar patients who responded to a specific therapy. The program searches the database to find similar patients and to quantitatively evaluate the effect of therapy given to each of them. In essence, the program attempts to emulate the processes of good clinical judgment by searching a database for

patients with identical diagnoses and covariates and who also have very similar hemodynamic patterns. The program then uses these “nearest neighbors’” as surrogates for the present study patient. The patient’s outcome may be estimated from the outcomes of the nearest neighbors who are known from the database. The predicted outcome of each patient on ED admission was validated by the patient’s actual outcome determined at hospital discharge several days or weeks later. Similarly, the prospectively determined therapeutic responses of the patient’s nearest neighbors were validated by the patient’s actual responses to the therapies.

A decision support system was developed to quantify the relative efficacy of each therapy used in each of the nearest neighbors in terms of SP improvement. The decision support system allows the clinician at the bedside to make choices based on knowledge of each therapy’s probability of improving outcome for the study patient’s unique circumstances.

This approach was tested in severely traumatized emergency patients in an inner-city public hospital. Under these circumstances, the survival probability was found to track clinical changes and changes after therapy throughout the observation period. Moreover, during the initially monitored resuscitation, the program correctly predicted outcome in about 90% of trauma patients during their first 24 hrs of resuscitation. Thus, the mathematical analysis and decision support program provides an independent tool to evaluate objectively both outcome and therapeutic responses.

The proposed approach was designed to provide an initial ED assessment of the likelihood of survival based on the clinical diagnosis, covariates, and noninvasive hemodynamic pattern. The reasons for favorable or unfavorable outcome predictions are apparent from the hemodynamic patterns. The therapeutic choices based on known responses of very similar patients in the database provide the attendants with a menu of therapies to consider together with their likely effects. If further studies confirm these results, the SP and therapeutic decision support program may provide a feasible method to objectively manage acute emergency patients.

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Key Words: noninvasive hemodynamic monitoring; cardiac index; mean arterial blood pressure; heart rate; pulse oximetry; transcutaneous oxygen and carbon dioxide tensions; outcome prediction; therapeutic decision support system

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Meta-analysis of hemodynamic optimization in high-risk patients *

[Feature Articles]

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Outline

Graphics

Abstract^

Objective: The aim of this evidence-based report was to review pertinent randomized controlled studies that describe hemodynamic goals in acute, critically ill patients and to evaluate outcome of resuscitation therapy in association with physiologic, clinical, and therapeutic influences.

Methods: MEDLINE was the source of randomized controlled studies written in English. The inclusion criteria were acutely ill, high-risk elective surgery, trauma, and septic patients. The goals of therapy were to resuscitate to either normal or supranormal values; the latter were described as a cardiac index of >4.5 L·min-1·m-, pulmonary artery occlusion pressure of <18 mm Hg, oxygen delivery of >600 mL·min-1·m-, and oxygen consumption of >170 mL·min-1·m-. The outcome criterion was survival or death. We found 21 randomized clinical trials described in 20 articles. The studies were divided into groups based on the time that goals were implemented (i.e., “early,” 8 to 12 hrs postoperatively or before organ failure, vs. “late,” or after onset of organ failure) and the severity of illness, determined by the control group mortality as >20% (12 studies) or <15% (nine studies).

Results: In severely ill patients (control mortalities group >20%), six studies had a 23% mortality difference ($p < .05$) between the control and protocol groups with early optimization, but seven studies optimized after the development of organ failure did not have significantly improved mortality. Moreover, outcome was not significantly improved in less severely ill patients (control

mortalities group <15%) and normal values as goals or when therapy did not improve oxygen delivery.

Conclusion: Review of 21 randomized controlled trials with various approaches to treatment revealed statistically significant mortality reductions, with hemodynamic optimization, when patients with acute critical illness were treated early to achieve optimal goals before the development of organ failure, when there were control group mortalities of >20% and when therapy produced differences in oxygen delivery between the control and protocol groups.

Goal-directed studies with the pulmonary artery catheter (PAC) are highly controversial. Many studies showed no advantage of the PAC in cardiac and other medical conditions or in postoperative patients admitted to the ICU after organ failures had developed (1–5). However, other investigators (6–21) reported that early, optimally increased cardiac index (CI) and oxygen delivery (·Do2) <12 hrs after surgery or 24 hrs after trauma were associated with improved survival. However, a evidence-based meta-analysis by Heyland et al. (22) showed that the attainment of supranormal hemodynamic goals did not significantly reduce mortality in critically ill patients. Recently, two consensus conferences also found insufficient evidence to fully determine whether PAC-guided therapy significantly alters outcome, but they did not consider time factors; by mixing early and late studies together, they concluded there were no significant differences in optimizing hemodynamic variables (23–25). In an insightful meta-analysis, Boyd (18) found no outcome improvement in seven prospective randomized studies of patients who entered the ICU after organ failure or sepsis had occurred (4, 5, 9, 11, 25, 26), but they noted significant outcome improvement in six other randomized studies when PAC-directed therapy was given early or prophylactically, that is, before organ failure or sepsis occurred (6, 7, 12, 14, 16, 17). Two recent studies also showed improved outcome with early goal-directed therapy (19, 20), suggesting that early optimization of ·Do2 and oxygen consumption values in high-risk surgical patients improves outcome. If, in some clinical circumstances, the hemodynamic values of survivors may be compensatory responses that have survival values, it is important to identify clinical conditions that may be appropriate for this type of goal-directed therapy. Second, it may be even more important to define therapeutic goals relative to the primary diagnosis and age; the presence of diabetes, hypertension, chronic cardiac and respiratory illnesses, and other co-morbid conditions; and the severity of illness, timing of therapy, dose ranges, and other limitations of this approach.

Evidence-based studies have become the standard for testing important therapeutic questions, but evaluation of a therapeutic intervention should be clearly related to the central scientific idea defined by the research plan. As a prerequisite for clinical trial evaluation, important aspects of experimental study designs should be considered, including: definition of diagnostic categories; timing and dose of the therapeutic modality being evaluated; the patients' age, sex, and severity of illness; the presence of significant co-morbid conditions; and the clinical setting (Shoemaker WC, Bayard DS, Botnen A, et al., unpublished observations) (27, 28).

Clearly, lack of comparability of studies because of differences in the experimental design may preclude meaningful meta-analysis. Sweeping conclusions can hardly be justified by amassing many studies with large numbers of patients when the design features of the studies are not appropriately considered. Major questions include: In goal-directed therapy, are there outcome differences in the use of normal values compared with the supranormal values of survivors? What roles are played by time factors, various associated clinical conditions such as organ failures, mortalities of the control groups, and differences in therapy between control and protocol arms? Is there a single optimal hemodynamic goal for all critically ill patients, or does

this depend on age, severity of illness, physiologic reserve capacities, organ failures, and other co-morbid conditions?

The present study reviewed 21 randomized clinical trials described in 20 articles to evaluate various influences that may contribute to outcome. Inclusion criteria of this meta-analysis were randomized clinical trials of high-risk elective surgery, trauma, and acute medical sepsis. We evaluated the definition of optimal therapy, time of optimization, age, types of illness, and severity of illness. The latter, for example, was defined by the mortality rate of the control group. The differences in mortality rates in the control and protocol groups were the main criteria for evaluation of therapeutic goals in various clinical circumstances, including acute illness, high-risk surgery, or trauma vs. chronic medical illnesses, the time that the therapeutic goals were implemented during the course of acute illness, and the presence or absence of organ failures. Hemodynamic values were used to evaluate the extent or aggressiveness of therapy to achieve the targeted protocol goals compared with the same therapy given to achieve the normal control goals. The differences between control and protocol groups were principally CI and ·Do2 because these have been reported to differentiate early survivor from nonsurvivor patterns (6–8, 27).

METHODS^

A search strategy was developed with the assistance of a research librarian. The database for references was MEDLINE, and the search was limited to include only references in English. The study design included randomized clinical trials of supranormal CI, pulmonary arterial occlusion pressure of <18 mm Hg, and ·Do2 and oxygen consumption indexed as therapeutic goals. The search terms that identified the most acceptable references were supranormal oxygen, resuscitation endpoints, cardiac output, oxygen delivery, oxygen consumption, survival and nonsurvival, and hemodynamics. The search identified 72 references; 52 of these were rejected after screening because of irrelevant interventions, patient populations, or outcome definitions.

Three inclusion criteria were used to define the patient populations, therapeutic goals, and interventions. These were: 1) critically ill patients after high-risk elective surgery, severe trauma, and septic shock; 2) therapeutic goals for resuscitation and subsequent management were either normal hemodynamic values or supranormal values observed in previous series of survivors and specified as a CI of >4.5 L·min-1·m-2, pulmonary arterial occlusion pressure of <18 mm Hg, ·Do2 of >600 mL·min-1·m-2, or oxygen consumption of >170 mL·min-1·m-2 (6–8, 18, 27); and 3) initial intervention was fluid therapy, and if hemodynamic targets were not achieved, inotropes were then added. Twenty references, with 21 studies, were reviewed and accepted for meta-analysis (Table 1). Experimental designs of the studies revealed at least four different categories of patients or therapeutic regimens. These included normal vs. supranormal therapeutic goals, early vs. late administration of therapy to achieve the stated goals, and differences in severity of illness determined by the control group mortality. Late was arbitrarily defined as >12 hrs after surgery, 24 hrs after injury, or after occurrence of an organ failure.

Table 1. Evidence for 21 studies and 20 articlesOF, organ failure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; [Latin capital letter D with dot above]o2, delivery of oxygen index; ICU, intensive care unit; S¯vo2, mixed venous oxygen saturation; ARDS, acute respiratory distress syndrome; PAC, pulmonary artery catheters; [latin capital V with dot above]o2, oxygen consumption index; CABG, coronary artery bypass graft; CVP, central venous pressure; pHi, gastric intramucosal pH; PA, pulmonary artery; LVF, left ventricular function.aStudy design: randomized, concealed, and blinded were described as Y = yes, N = no, NC = not clear, and ND = no data.

Table 1. (Continued)

We used the following characteristics to evaluate the quality of these randomized studies. An optimum randomization process may have included a third party, a table of random numbers, or a computer-generated list to assign impaneled subjects to either the treatment or control arm. The assignment to a treatment arm was "concealed" if a third party or sealed envelopes were employed to assign subjects to the treatment or control arm. The process was "blinded" when both the investigators and the subjects were not aware of the patients' assignment to the control or protocol arm. Finally, the withdrawal or dropout analysis was adequate if the investigators identified the number of subjects excluded, provided an explanation for exclusion, and provided the number remaining for evaluation. If the authors did not describe these processes, it was assumed that they did not employ the preferred method, and the study design was not considered optimal. The minimum criterion for inclusion was proper randomization. If the processes for concealment, blinding, or withdrawal or dropout were not described or verified by direct communication, these design components were scored as "not clear."

All studies reviewed were randomized. There were 15 studies (4–7, 9–11, 13, 15, 17, 19, 20, 29–32) on high-risk elective surgical patients, five of these included medical patients, and two of these studies also included trauma patients. Four studied only trauma patients (14, 16, 25, 29), and two studied septic (medical) patients (12, 25). Two studies were blinded to the investigators in terms of the fluid management; the other studies were not blinded. Table 1 lists the characteristics for each study.

The general variance-based method was used to calculate the summary statistic for the meta-analysis (33). The effect size calculated was the rate difference between the protocol group and the control group. The summary statistic was the rate difference between the groups. This method is based on the fixed-effects model. A significant p value was <.05.

RESULTS^

The results are expressed as the mortality rate difference and confidence limits, which are twice the sd. The mortality rate differences between control and protocol groups in the series as a whole varied from -0.35 to 0.2. The average mortality rate difference for all 21 studies was -0.05 + 0.02, indicating statistically significant improvement with the protocol groups for the series as a whole ($p < .05$). Table 1 lists the studies compiled from the literature in which either normal values or the optimal therapy, defined as CI > 4.5 L·min-1·m-2 and ·Do2 > 600 mL·min-1·m-2, was given to the protocol groups, and their mortalities were compared with their corresponding control groups given standard therapy. In seven studies, the values of the protocol groups reached the proscribed therapeutic goals in the allotted time frame.

Figure 1 illustrates the values of the 14 randomized studies whose control group mortalities were >20%. Seven early studies whose optimal therapy was completed before organ failure occurred had marked and significant overall reduction in the mortality rate of -0.23 + 0.07 ($p < .05$). Of the seven late studies of patients who had organ failure before initiation of the studies, the overall mortality rate difference was 0.01 + 0.06, indicating no significant improvement with therapy. In these seven studies, only the study of Yu et al. (11) of patients aged 50–75 yrs had improved outcome with optimized therapeutic goals.

Figure 1. Mortality differences between protocol and control groups with control group mortality of >20% (upper section) and <15% (lower section). Therapeutic goals are specified as

supranormal or normal hemodynamic values. Note for each study the first author's name, date of publication, number or randomized subjects, number of subjects evaluated as protocol vs. control groups, populations, mortality of the protocol patients minus control mortality, and the difference between protocol and control mortalities. Surg, surgery;Med, medical;Tra, trauma.

Figure 1 also illustrates mortality rate differences in three groups of studies with control group mortalities of <15% or normal values for therapeutic goals. The first group consisted of two studies with control group mortalities of 10% and 11%. One study (26) consisted of patients with organ failures before therapy, and the second study (27), which excluded patients who died within 24 hrs of admission, had a control group mortality of 11% and a protocol mortality of 15%, but there was no difference in ·Do2 between the control and protocol groups. The latter suggested that the treatment of control patients were similar to that of the protocol patients. If there were no differences in therapy, no outcome differences should be expected, and none were found. Neither of these studies showed significant differences in the mortality rates between the control and protocol groups; the combined rate difference of these two studies was 0.03 ± 0.11 ($p > .05$). The fourth group in Figure 1 studied partial hepatectomy in cirrhotic patients who had an 11% control group mortality but a protocol group mortality of only 0% (16). The rate difference of -0.11 did not reach statistical significance, probably because the sample size was only 34 patients. The last group consisted of five studies that used normal values as goals and had control mortalities of <11%. Their subtotal rate difference was -0.01 ± 0.03 ($p > .05$). The three groups (ten studies) had control group mortalities that were <15%, with a mean of 7.1%, suggesting that these patients were not as severely ill as the first two study groups whose mean control mortality was 42.1% (Fig. 1 and Table 1). In high mortality series, fewer patients are needed to show improved outcome with different therapeutic goals.

DISCUSSION^

Hemodynamic bedside monitoring by PACs has been considered by many as a standard for circulatory evaluation of critically ill patients, but its usefulness has recently been seriously questioned (1–5, 22–25), particularly in the late stages of illness after onset of multiple organ failures (23–25). The present review showed significantly improved outcome in randomized studies when PAC goal-directed therapy was administered early or prophylactically in patients who were optimized preoperatively and maintained in the intraoperative and immediate postoperative period.

Early studies using invasive ICU monitoring in randomized trials reported that increased CI and ·Do2 to values characteristic of survivors of high-risk surgery in the immediate postoperative period improved outcome (6). At the initial stage in the development of this concept, it was realized that the survivors of acute critical illnesses had a wide range of higher-than-normal hemodynamic values (6, 8, 10, 18, 19, 31, 34). Because it is not possible to test a range of values, the mean or median values were arbitrarily chosen as cutoff points, not to establish a set of optimal values but to test the hypothesis that critically ill patients have high metabolic rates and therefore require greater than normal hemodynamics and oxygen transport to sustain the increased body metabolism after trauma, surgery, or sepsis. Hemodynamic goals of surviving patients were proposed as a first approximation to optimal goals for the immediate postoperative period of high-risk surgical patients. These proposed optimal therapeutic goals were not intended to be generally applied to all patients at all times because metabolic requirements are affected by age, sepsis, blood loss, preexisting cardiac and pulmonary insufficiency, and other co-morbid conditions (10, 35). Ultimately, optimal goals may be calculated for each individual patient on the basis of his or her diagnosis, co-morbid conditions, past hemodynamic deficits, and temporal

stage. This is presently approached by using discriminate analysis (27) and stochastic control programs (28).

In the initial randomized trial of supranormal hemodynamic values, the mortality was decreased, but more importantly, the prevalence of organ failures was reduced from 31 cases in the control group to 1 case in the protocol group (6). Moreover, in a series of postoperative patients invasively monitored before the diagnosis of ARDS, the nonsurvivors' CI values were in the normal range; the survivors who developed ARDS had CI values that were significantly elevated (4 L·min-1·m-2) but less than the values of survivors who did not develop ARDS (4.5 L·min-1·m-2) (34, 38, 39). Before the onset of ARDS, the mean pulmonary artery occlusion pressures were within acceptable limits for critically ill postoperative patients and none had a pulmonary arterial occlusion pressure of >18 mm Hg. Bishop et al. (16, 39) reported that supranormal goals within 24 hrs of the injury reduced the prevalence of ARDS and other organ failures after severe trauma; they reduced mortality from 39% to 18% ($p < .05$) and reduced prevalence of organ failure from 105 in 65 control patients (1.62 ± 0.28 organ failures per patient) to 37 in 50 protocol patients (0.74 ± 0.28 organ failures per patient) ($p < .05$). Less than optimal values in the early stage may lead to inadequate total blood flow and uneven microcirculatory blood flow from uneven vasoconstriction of the adrenomedullary stress response (8, 34, 38–42). Local hypoxia and acidosis of the capillary endothelium from uneven capillary blood flow is known to stimulate the systemic inflammatory response system and lead to organ failure (41, 42).

The definition of early as opposed to late studies is necessarily arbitrary. Cutoff points for the patient to reach the designated goals were: the first 12 hrs postoperatively in elective surgery, 24 hrs after injury in trauma patients, and before the onset of an organ failure. When sepsis was the primary diagnosis, we accepted the definition of "early septic shock" proposed by Tuchschmidt et al. (12), which was within 4 hrs of the time of diagnosis. However, when sepsis was a complication of elective high-risk surgery, as in the studies of Yu et al. (9–11), it was arbitrarily designated as an organ failure or dysfunction and therefore classified as late. Of these three published articles (9–11), the 1998 publication that was a continuation of their earlier studies seems to include 47 of the 50 subjects that were evaluated in the 1995 article. Therefore, to avoid redundancy, the 1995 study was not included in this meta-analysis. In the 1993 study, Yu et al. (9) demonstrated that when both the protocol and control groups were aggressively hydrated to a pulmonary artery occlusion pressure of 15–18 mm Hg, the difference in the mortality rates was insignificant. In the interim study (1995), Yu et al. (11) observed that when the subjects in both the protocol and control groups who generated a ·Do2 of >=600 mL·min-1·m-2 after fluid resuscitation were excluded from the study, the mortality rate of the remaining protocol subjects was significantly less than the remaining control subjects. This difference was associated with the administration of inotropes and vasoactive drugs given to the protocol group to achieve a ·Do2 of >=600 mL·min-1·m-2. In the 1998 study, Yu et al. (10) evaluated the larger series of patients randomized to protocol and control groups, and stratified the groups according to age: <=75 yrs (50–75 yrs of age) and >75 yrs. All subjects who achieved a ·Do2 of >=600 mL·min-1·m-2 after fluid resuscitation were excluded. The mortality rate of the protocol group of the subjects aged <=75 yrs was significantly less than the control group. However, the mortality rate in the protocol and control groups of subjects aged >75 yrs was not different ($p > .05$). These findings suggest that the subjects aged >75 yrs did not effectively respond, in terms of outcome, to aggressive vasoactive drugs or inotropes.

In the study of Wilson et al. (19), patients undergoing major elective surgery were randomized into three groups; two groups of 42 patients received invasively monitored fluid and either adrenaline or dopexamine to increase ·Do2, whereas the third group of 42 patients received

routine postoperative care and served as the control. Only 3 of 92 patients (3%) in the optimized groups died, whereas 8 of 46 patients (17%) in the control group died ($p < .007$). The length of stay of the dopexamine group was significantly reduced compared with both the adrenaline group ($p = .02$) and the control group ($p = .009$). The authors concluded that because of the low doses of inotropes, fluid optimization was a major contributor to improved ·Do2 and improved outcome in their patients (19).

Three randomized trials not included in this meta-analysis deserve mention. In a study by Takala et al. (36) of postoperative patients with 13% control mortality that used relatively normal values as goals, patients were initially brought into the normal hemodynamic range, and then two dosage levels of dopexamine were tested in randomized trials, but the outcome was not significantly improved. Sinclair et al. (37) studied length of hospital stay in patients with proximal femoral fractures after optimizing stroke volume with repeated colloid fluid challenges measured by esophageal Doppler ultrasonography. They demonstrated significantly reduced hospital stay, but there was insignificant reduction in mortality because of only two deaths in the control group and one death in the protocol group. Polenen et al. (43) used mixed venous oxygen saturation and lactate levels as criteria for adequacy of resuscitation immediately postoperatively in 403 cardiac surgical patients. The median hospital stay was shorter in the protocol group (6 vs.7 days, $p < .05$), and morbidity was significantly less at the time of hospital discharge (1.1% vs. 6.1%, $p < .01$), but mortality was very low and not significantly affected by the study.

Low control mortalities suggest that the patients were not very ill and therefore may not respond as clearly to increased hemodynamics and, at the same time, may require much larger numbers of patients to show statistical significance. In the studies of Mythen et al. (17) and Ueno et al. (15), the protocol patients given therapy to achieve optimal goals had 0% mortalities, but because of the small number of patients, statistical significance was not achieved. Moreover, in the study of Berlauk et al. (13), the mortality was reduced from 9.5% in the control group to 1.5% in the optimized group, which was not significant; however, the number of complications were significantly reduced.

Similarly, if the control and protocol patients were treated in a similar manner, no differences in outcome should be expected. In the study of Velmahos et al. (29), the difference in ·Do2 between control and protocol patients was not statistically significant because the treatment of control and protocol patients were not different, and therefore, the mortality was, not unexpectedly, not different.

We conclude that increased CI and ·Do2 with pulmonary arterial occlusion pressure of <18 mm Hg should be considered as goals of therapy. When implemented early and aggressively, this reduces mortality and the prevalence of organ failures in acute postoperative and posttrauma conditions. Goal-directed therapy to achieve optimal goals is ineffective in the late stages after onset of organ failure because no amount of extra oxygen will restore irreversible oxygen debts, failed organs, or dead cells. In the late stage of acute illness after organ failure has occurred, aggressive therapy directed toward achieving the survivors' supranormal values is futile. When oxygen debt is no longer reversible, increased oxygen transport is not effective. Moreover, it is difficult to demonstrate significant changes after optimization when there are no significant differences between therapy given to the control and protocol groups. That is, there must be significant differences in the type of therapy or the amount of therapy given to expect significant outcome improvement. Furthermore, outcome differences may be extremely difficult to demonstrate when the patient population is not very ill, as indicated by control mortalities of

<15%. Finally, no effect should be expected in chronic medical conditions in which physiologic compensations have already had their maximum effect.

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FOOTNOTES^

*See also p. 1909. [Context Link]

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Key Words: noninvasive hemodynamic monitoring; bioimpedance cardiac output; thermodilution cardiac output; pulse oximetry; transcutaneous oxygen and CO2 monitoring; trauma; high-risk surgery; acute septic shock; therapeutic hemodynamic goals; organ failure

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Local Messages On Shelves At: Norris(all yrs),GenHosp,CHLA., Online Access: since 1996
Abstract The mathematical model satisfactorily predicted outcome in acute emergencies based on noninvasively monitored flow, pressure, pulse oximetry, tissue perfusion values, and their cumulative deficits. A decision support system provided information on the relative effectiveness of various therapeutic modalities based on the responses of patients with very similar states. The concept that hypovolemia and oxygen debt is an early primary problem that plays an important role in low flow and poor tissue perfusion states is supported by direct observation of massive hemorrhage, estimated blood loss of hemoperitoneum and hemothorax at the time of surgery, and prior studies in the literature that documented blood volume deficits in posttraumatic and postoperative patients who subsequently developed organ failures and death.
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Outcome Prediction of Emergency Patients by Noninvasive Hemodynamic Monitoring*

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Abstract

Objectives: We used noninvasive hemodynamic monitoring in the initial resuscitation beginning in the emergency department (ED) for the following reasons: (1) to describe early survivor and nonsurvivor patterns of emergency patients in terms of cardiac, pulmonary, and tissue perfusion deficiencies; (2) to measure quantitatively the net cumulative amount of deficit or excess of the monitored functions that correlate with survival or death; and (3) to explore the use of discriminant analysis to predict outcome and evaluate the biological significance of monitored deficits.

Methods: This is a descriptive study of the feasibility of noninvasive monitoring of patients with acute emergency conditions in the ED to evaluate and quantify hemodynamic deficits as early as possible. The noninvasive monitoring systems consisted of a bioimpedance method for estimating cardiac output together with pulse oximetry to reflect pulmonary function, transcutaneous oxygen tension to reflect tissue perfusion, and BP to reflect the overall circulatory status. These continuously monitored noninvasive measurements were used to prospectively evaluate circulatory patterns in 151 consecutively monitored severely injured patients beginning with admission to the ED in a university-run county hospital. The net cumulative deficit or excess of each monitored parameter was calculated as the cumulative difference from the normal value vs the time-integrated monitored curve for each patient. The deficits of cardiac, pulmonary, and tissue perfusion functions were analyzed in relation to outcome by discriminant analysis and were cross-validated.

Results: The mean (± SEM) net cumulative excesses (+) or deficits (-) from normal in surviving vs nonsurviving patients, respectively, were as follows: cardiac index (CI), +81 ± 52 vs -232 ± 138 L/m2 ($p = 0.037$); arterial hemoglobin saturation, -1 ± 0.3 vs -8 ± 2.6%/h ($p = 0.006$); and tissue perfusion, +313 ± 88 vs -793 ± 175, mm Hg/h ($p = 0.001$). The cumulative mean arterial BP deficit for survivors was -10 ± 13 mm Hg/h, and for nonsurvivors it was -57 ± 24 mm Hg/h ($p = 0.078$).

Conclusions: Noninvasive monitoring systems provided continuously monitored on-line displays of data in the early postadmission period from the ED to the operating room and to the ICU for early recognition of circulatory dysfunction in short-term emergency conditions. Survival was

predicted by discriminant analysis models based on the quantitative assessment of the net cumulative deficits of CI, arterial hypoxemia, and tissue perfusion, which were significantly greater in the nonsurvivors.

Key Words: hemodynamic monitoring • multicomponent noninvasive circulatory monitoring • outcome prediction • pulse oximetry • temporal hemodynamic patterns • transcutaneous oxygen tension

Introduction

Hemodynamic bedside monitoring by pulmonary artery catheters (PACs) has been considered by many as the "gold standard" for critically ill patients, but its usefulness has been challenged,[1] [2] [3] [4] [5] [6] [7] particularly in the late stages of illness after the onset of organ failures. A meta-analysis by Boyd and Hayes[8] showed no outcome improvements in seven randomized studies of patients who entered the ICU after organ failure or sepsis had occurred, but there was significantly improved outcome in six other randomized studies, plus two more recent studies,[9] [10] when PAC-directed therapy was given early or prophylactically. Since time may be important in the initial resuscitation and management of emergency patients, noninvasive monitoring is proposed as an alternative approach to identify and correct hemodynamic deficiencies at the earliest possible time. Previous studies have documented satisfactory correlation between thermodilution and bioimpedance cardiac output values for trauma patients in the emergency department (ED), the operating room (OR), and the ICU. The mean (± SEM) bias and precision in the ED were -0.058 ± 0.78 L/min/m2.[11]

In the present study, we monitored severely injured emergency patients, beginning in the ED and continuing in the radiology department, the OR, and then in the ICU. Acute injury was studied because time factors are important and the time course of circulatory events could be monitored from the time of hospital admission.[11] [12] Continuous visual displays of monitored data were used to evaluate rapidly changing patterns during unstable emergency conditions. Second, we time-integrated the differences between the monitored curve and normal values or reference values reflecting "optimal" goals derived from the patterns observed throughout the time course of previous series of survivors of acute severe illnesses or operations.[13] [14] [15] [16] [17] [18] [19] [20] [21] We then calculated the net cumulative excesses or deficits of each monitored variable for each patient and for the survivors and nonsurvivors. Finally, we explored the use of discriminant analysis to predict outcome based on these calculated cumulative deficits.

Materials and Methods

Clinical Series

We satisfactorily studied 151 of 155 consecutively monitored major trauma patients with noninvasive circulatory monitoring beginning shortly after their admission to the ED and continuing into the radiology department, the OR, through the postanesthesia recovery area, and to the ICU. Four patients were excluded because of insufficient data due to technical equipment failure or communication issues with personnel; the present report describes the data of 151 patients. Table 1 lists the salient clinical features of the series. Patients with major blunt trauma or penetrating trauma and significant risk of mortality or morbidity were selected for monitoring prior to possible emergency surgery. The criteria for resuscitation were empirically determined by the previous series of survivors' values and by the best possible initial responses of the

cardiac index (CI) and the other hemodynamic variables.12 13 14 Monitoring was continued until a plateau was reached after vigorous fluid and inotropic therapy resuscitation or until 24 h had elapsed. Optimal hemodynamic goals were sought, in so far as possible, but the adequacy of initial resuscitations may have been limited in part by clinical exigencies at the time. The calculation of cumulative excesses or deficits and discriminant analysis were performed after monitoring was completed. The institutional review board approved the protocol.

Table 1. Clinical Features *

Mean Arterial BP

Continuous mean arterial BP (MAP) was measured noninvasively (Dynamap system; Criticon; Tampa, FL) or was calculated electronically from transducers in line with intra-arterial catheters when the latter were used.

Cardiac Output

A thoracic bioelectric impedance device (IQ system; Wantagh Inc; Bristol, PA) was applied shortly after the arrival of the patient in the ED. Pairs of noninvasive, disposable, prewired hydrogen electrodes were positioned with one pair placed on each side of the base of the neck and two other pairs placed one on each side of the chest at the level of the zyphisternal junction opposite the lateral axillary line. Three ECG leads were placed across the precordium and left shoulder.22 23 A 100-KHz, 4-mA alternating current was passed through the patient's thorax by the outer pairs of electrodes, and the voltage was sensed by the inner pairs of electrodes; the voltage sensed by the inner electrodes captured the baseline impedance, the first derivative of the impedance waveform, and the ECG. The ECG and bioimpedance signals were filtered with an all-integer-coefficient technology to decrease computation and signal-processing times. The signal-processing algorithm used a time-frequency distribution (modified Wigner distribution) analysis that increased signal-to-noise ratios.22 23 The data were automatically acquired and downloaded to a floppy disk. When indicated by clinical criteria, PACs were inserted into the patient in the OR or the ICU, and CI estimations were made at least hourly in unstable patients and every 4 h in stable patients. The optimal goal for CI in various etiologic diagnostic groups was defined by survivors' values12 13 14 and was tested in subsequent studies.14 15 16 17 18 19 20 21

Limitations of the impedance method include faulty electrode placement, motion artifacts, restlessness, shivering, pulmonary edema, pleural effusion, valvular heart disease, dysrhythmias, and electrical leaks from other instruments using the same circuit. These are usually apparent from inspection of the impedance waveform and by the following previously described criteria: baseline impedance > 15 ohms and impedance signal > 0.3 ohm, which usually indicate pulmonary edema due to cardiac failure or late-stage ARDS.11 These limitations were excluded during the time of monitoring in the present study.

Pulse Oximetry

Arterial oxygen saturation (SaO2) was assessed continuously by pulse oximetry (Nellcor; Pleasanton, CA) as a reflection of pulmonary gas exchange. Values were observed and recorded at the time of the CI measurements. Appreciable or sudden changes in these values also were noted, and changes to < 94% were confirmed by SaO2 measurement obtained by standard blood gas analysis.11 12

Transcutaneous Oxygen Tension

Standard transcutaneous oxygen tension (tcPO2) measurements were continuously monitored throughout the observation period. This technology uses the same Clark polarographic oxygen electrode routinely employed in standard blood gas measurements.[24] [25] [26] [27] [28] [29] The oxygen tensions were measured in a representative area of the skin surface heated to 4°C to increase diffusion of oxygen across the stratum corneum and to avoid vasoconstriction in the local area of the skin being measured.[27] Previous studies demonstrated the capacity of transcutaneous oxygen tensions to reflect tissue oxygen tension.[11] [12] [25] [28] tcPO2 has been shown to reflect the delivery of oxygen to the local area of skin; it also parallels the mixed venous oxygen tension except under late or terminal conditions in which peripheral shunting leads to high mixed venous hemoglobin saturation values.[24] While oxygen tension of a segment of the skin does not reflect the state of oxygenation of all tissues and organs, the skin has the advantage of being the most sensitive early warning tissue of the adrenomedullary stress response; vasoconstriction of the skin is an early stress response to hypovolemia and other shock syndromes.[11] [12] [24] tcPO2 Values were indexed to the fraction of inspired oxygen (FIO2) concentration to give a tcPO2/FIO2 ratio because of marked tcPO2 changes produced by changes in the level of inspired oxygen. The thermal environment was maintained at reasonably constant levels, and marked changes in room temperature from drafts or open windows were avoided to maintain the accuracy of the transcutaneous methods. In addition, the electrode must be moved to a nearby thoracic or shoulder site every 4 h and recalibrated to avoid first-degree skin burns.

Level of Consciousness

At the time of the patient's admission to the ED, the clinical team evaluated and recorded the degree of unconsciousness by the Glasgow coma scale (GCS), which uses eye movement, verbal responses, and motor responses to verbal and painful stimuli. The clinical service also noted changes in the GCS throughout the patient's hospital course.

Estimated Blood Loss at the Time of Surgery

Blood loss was estimated by the surgeon and anesthesiologist intraoperatively in a routine manner by counting lap tapes and sponges and by measuring the contents of suction bottles.

Method for Calculating the Total Cumulative Excess or Deficit of Each Monitored Variable

The patterns of each patient were examined for motion artifact, noise, effects of fluid and vasopressor therapy, manipulation of tubing, and other extraneous factors. The total overall deficit or excess of each noninvasively monitored variable was evaluated by comparing its normal or optimal value with its temporal pattern during the observation period. This was done by mathematically integrating over time the area between the continuous display of each fluctuating variable and either the normal values for BP, SaO2, and tcPO2/FIO2 or the optimal goal, as defined by the CI values of survivors during the first 24 h after hospital admission.[11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21]

The net cumulative deficits or excesses were calculated for each individual patient and for both survivor and nonsurvivor groups as time-integrated areas between the curve produced by continuously monitored variables and their normal or reference values. For example, given a normal MAP of 85 mm Hg, in a patient whose MAP averaged 60 mm Hg for 2 h before resuscitation, the calculated deficit is -50 mm Hg/h ([85–60] x 2).

Flow calculations, measured as volume per unit of time, are in liters per minute per square meter. When multiplied by the monitored time in minutes, this gives, as units, liters per square meter for CI or liters for cardiac output. The units for MAP, SaO2, and tcPO2/FIO2 are millimeters of mercury per hour, percent per hour, and millimeters of mercury per hour, respectively.

When the mean MAP deficits were calculated using all values, a large number of normal high values obscured the deficits; the patients with cardiac arrest and zero MAP, for example, showed no net MAP deficit, because the many normal and high values overshadowed the later short but lethal hypotensive episode. For MAP, therefore, we calculated cumulative deficits from decreases below the normal range.

Statistical Analysis

The survivors' and nonsurvivors' deficits of MAP, CI, SaO2, and tcPO2/FIO2 were calculated for the periods of monitoring. Each of the categoric variables was tested for the difference in distributions between the two outcome groups, those who survived and those who died during the current hospitalization, using the {chi}2 test or two-tailed Fisher's Exact Test. The t test with Bonferroni correction was applied to each of the continuous variables to compare the means of the two outcome groups. Variables considered for discriminant analysis were CI, GCS, SaO2, tcPO2/FIO2, MAP, heart rate, PaO2, hematocrit, transcutaneous CO2 tension (PtcCO2), injury severity score, age, and gender. The first four met the criteria ($p < 0.20$).

The variables that were significant at the $p < 0.2$ level by the aforementioned {chi}2 tests or the t tests were fed into a stepwise discriminant analysis (PROC STEPdisk) to identify the variables that collectively contribute to differentiate the two outcome groups. Thus, the variables selected then were entered into a model in PROC DISCRIM to derive the discriminant function by generalized squared distance, taking into account the prior probabilities of the groups. This procedure evaluated the discriminant function by calculating the error rate estimates or the probabilities of misclassification.

Cross-validation of the results was performed by the jackknife method. The data were split into two independent samples by taking the data of every other patient. One group was used for calibration to generate another series of classification functions, and the remaining group was used to calculate results based on the new classification functions. The statistical analyses were performed with a computer program (SAS for Windows, Release 6.12; SAS Institute; Cary, NC).

Noninvasive Monitoring From the Time of Admission

The use of noninvasive monitoring systems was found to be feasible in patients experiencing short-term emergency conditions for the early description of temporal hemodynamic patterns and to provide quantitative calculations of the total amount of deficit or excess accumulated by each monitored variable. There were 103 survivors and 48 nonsurvivors (mortality rate, 32%), 131 patients were men, 20 patients were women, and the average (± SEM) age was 35 ± 1.4 years. Of 61 patients with gunshot wounds, 42 survived and 19 died (mortality rate, 31%). Of 68 patients with blunt trauma, 41 survived and 27 died (mortality rate, 40%). Of 22 patients who sustained stab wounds, 20 survived and 2 died (mortality rate, 9%). Of 41 patients who had head injuries, 24 survived and 17 died (mortality rate, 41%). Of 68 patients who sustained chest injuries, 50 survived and 18 died (mortality rate, 26%). Of 84 patients who sustained abdominal injuries, 54 survived and 30 died (mortality rate, 36%). Sixty-eight patients had injuries involving more than one bodily area. The injury severity score (± SEM) was 21.8 ± 4.7 for survivors and 30.5 ± 4.6 for nonsurvivors ($p = 0.24$).

Monitoring was performed for 7.9 ± 2.6 h during the initial resuscitation (survivors, 7.8 h; nonsurvivors, 8.3 h). Subsequently, survivors were monitored intermittently to 15.6 ± 7.1 h after hospital admission, and nonsurvivors were monitored to 18.7 ± 8.4 h after hospital admission.

The data of emergency patients from the time of their ED admission are shown in Figure 1 . The correlation between simultaneous thermodilution and bioimpedance cardiac output measurements in the present series was r = 0.91 and r2 = 0.83, and bias and precision were -0.30 ± 1.10 L/min/m2. Table 2 lists the mean ± SEM of CI, MAP, SaO2, and tcPO2/FIO2 for survivors and nonsurvivors averaged throughout the observation period. The CI, SaO2, and tcPO2/FIO2 values of patients who survived were significantly greater than for those who died. MAP values of survivors tended to be higher than those for nonsurvivors (p = 0.066) (Table 2) .

Figure 1. The temporal patterns of survivors (solid line) and nonsurvivors (dashed line) for MAP, CI, SaO2 (SapO2), and tcPO2 (PtcO2) indexed to the tcPO2/FIO2 ratio. All values are keyed to the time of admission to the ED. Dots represent mean values, and vertical lines represent SEM. Cross-hatched areas indicate the normal range for MAP, SaO2, and tcPO2/FIO2 ratio and optimal goals for CI. Note that the CI, MAP, SaO2, and tcPO2/FIO2 values of survivors were generally higher than those of the nonsurvivors.

Table 2. Noninvasive Hemodynamic Values for Survivors and Nonsurvivors *

The body temperatures of survivors and nonsurvivors at hospital admission averaged 36.7 ± 0.0°C to 7°C and 36.3 ± 0.0°C to 9°C, respectively. We took aggressive precautions to correct hypothermia when it occurred, especially in the OR where conditions were more controllable.

The mean (± SD) estimated blood loss, which reflects preoperative and intraoperative hemorrhaging, measured 2,970 ± 3,856 mL in survivors and 6,263 ± 5,540 mL in the nonsurvivors at the end of surgery. In the present series, there were 22 patients who had massive blood loss (ie, > 5,000 mL). Vigorous attempts were made to replace these losses at the time of surgery and in the immediate postoperative period.

Temporal Circulatory Patterns in Survivors and Nonsurvivors

Figure 1 shows the temporal patterns of noninvasive circulatory variables of the survivors and nonsurvivors beginning with the initial measurements after admission to the ED. CI values were initially higher in the survivors. The SaO2 values of nonsurvivors were significantly lower than the those of survivors, but these differences were not clinically important; when SaO2 reductions occurred, they were rapidly corrected by intubation, mechanical ventilation, or increased FIO2. The values for the tcPO2/FIO2 ratios of nonsurvivors were markedly lower than those of survivors and were lower than normal throughout the observation period. Table 3 lists the time taken to achieve goals of therapy for each variable that reached the desired end point as well as the number and percentage of those who did not reach the goals. The deaths of nonsurvivors occurred an average of 8.7 ± 2.8 days after hospital admission. However, there was a bimodal distribution with 17 deaths in the first 8 h and 14 deaths occurring >= 10 days after hospital admission.

Table 3. Time to Reach Goal in Patients Who Attained Goal *

Net Cumulative Amount of Deficit or Excess in Monitored Variables

Table 4 shows the net cumulative deficit or excess of monitored variables used to evaluate cardiac, pulmonary, and tissue perfusion functions. Figure 2 is an illustrative example of a survivor whose CI and tissue perfusion deficiencies were corrected at 19 and 23 h postadmission, respectively. Figure 3 shows the data of a patient whose CI and tissue perfusion deficiencies persisted for > 24 h. He developed lethal ARDS.

Table 4. Mean Net Cumulative Deficits or Excesses of Monitored Values of Survivors and Nonsurvivors Throughout the Period of Observation

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Figure 2. Data of a 64-year-old man who was hit by a car and sustained fractures of the pelvis, open left femur, left tibia, and fibula, and dislocation of the knee. He was given 6 U packed RBCs and 5,000 mL crystalloids in the ED. In the angiographic suite, he was given 6 more units of packed RBCs, 5 U fresh frozen plasma, and 2,000 mL crystalloids. His CI values became optimal (ie, 4 L/min/m2) by about 18 h, and his tcPO2/FIO2 values reach the normal range in 24 h. The patient lived. See the legend of Figure 1 for abbreviations not used in the text.

Figure 3. Data from a 26-year-old man who sustained multiple stab wounds of the abdomen with lacerations of the stomach, duodenum, and superior mesenteric vein. He had marked reduction of cardiac output and tissue perfusion despite the administration of 48 U packed RBCs, 5 U whole blood, 12,500 mL lactated Ringer's solution, 10 U platelets, 13 U fresh-frozen plasma, and 1,000 mL hetastarch, in addition to dobutamine and dopamine infusions for an estimated 18,000-mL blood loss. The patient died of ARDS and multiple organ failure. See the legend of Figure 1 for abbreviations not used in the text.

Outcome Prediction

There were significantly greater calculated deficits of CI, pulse oximetry, and transcutaneous O2 in nonsurvivors than in survivors during the period of monitoring (Fig 4 and Table 4). These three variables and the GCS, having moderate levels of significance with outcome, were selected for the stepwise discriminant analysis (PROC STEPdisk). Based on the classification function generated for each of these four variables in PROC DISCRIM, the discriminant function, Z, was derived:

where a represents cumulative tcPO2/FIO2 values, b represents the GCS, c represents cumulative SaO2 values, and d represents cumulative CI values. Table 5 summarizes the relative influence of each variable with respect to outcome. Ninety-five percent of the survivors and 62% of the nonsurvivors were correctly classified in the first 24 h postadmission (Table 6). Of 151 patients, 23 (15.2%) were misclassified. Five of the 35 patients predicted to die in the first 24 h subsequently improved and lived.

Figure 4. Cumulative excesses and deficits in survivors and nonsurvivors for CI and tcPO2/FIO2 calculated for the monitored period. See the legend of Figure 1 for abbreviations not used in the text.

Table 5. Stepwise Discriminant Analysis *

Table 6. Classification Summary for the Series (n = 151) *

Results of Cross-Validation

Cross-validation of the discriminant analysis by the jackknife method demonstrated results that were similar to the initial calculation for the series as a whole. The results of the calibration data set (N = 75) are shown in Table 7 , and the results from the validation data set (N = 76) are shown in Table 8 . The cross-validated discriminant analysis was

Table 7. Classification From the Calibration Dataset (n = 75) *

Table 8. Classification From the Validation Dataset (n = 76) *

where a, b, c, and d are defined as above. The classification of the survivors was $Z > 1.91$. Miscalculations occurred in 12 of 76 patients (16%). This was considered to be in satisfactory agreement with the initial calculation and suggests consistency of the data by this analysis.

The limitations of noninvasive bioimpedance cardiac output monitoring include motion artifacts, arrhythmias, pulmonary edema, pleural effusions, and expansion of interstitial fluid from massive crystalloid infusions. The advantages of this noninvasive monitoring system include technical convenience and the continuous display of data allowing the calculation of the amount of deficit or excess of each variable from the time-integrated area under the curve. The area under the curve provides an arithmetic solution to replace the subjective evaluation of irregular curves and provides estimates of cardiac, pulmonary, and tissue perfusion functions.

The net cumulative deficits of flow and tissue perfusion measured during the initial resuscitation period were greater in nonsurvivors than survivors; these differences were correlated with outcome. For example, during the monitoring period, the CI values of survivors averaged 81 L/m2 more than the optimal 4.0 L/min/m2, which was determined empirically from the plateau of high values of survivors within the first 24 h of hospital admission.11 12 13 14 15 16 17 18 19 20 21 This was equivalent to 140 L of cardiac output per patient over the monitored period. During the monitoring period of those who died, the CI averaged 232 L/m2 less than optimal, and the cardiac output averaged 402 L per patient less than optimal. The difference between survivors and nonsurvivors was 542 L. We used 4.0 L/min/m2 as the therapeutic goal because this was the mean value for the first 24-h period, on which this study was focused. This goal admittedly is arbitrary and points to the need for additional research in this area.

The high early CI values in survivors suggest that there may have been less hypovolemia and/or better physiologic compensations. This concept is reinforced by the greater tcPO2/FIO2 net cumulative excesses, which suggest better tissue perfusion/oxygenation for survivors in the initial stages. These preliminary studies need to be evaluated independently in larger series with different types of acute illnesses and emergency conditions. Furthermore, additional studies are needed to evaluate the effects of specific trunk and extremity traumas, head injuries, pelvic and long bone fractures, prior organ dysfunctions, and other comorbid states on the validity of this early predictive model.

The hypothesis underlying this approach is that circulatory deficiencies that ultimately lead to shock, organ failure, and death may be identified early by noninvasive monitoring even in the extenuating circumstances of severely traumatized emergency patients in a large inner city public

hospital. Earlier diagnosis of a circulatory deficiency allows therapy to be initiated sooner in the hope that earlier therapy may improve outcome in emergencies where time is crucial.

More importantly, noninvasive monitoring, which has been reported to be easy, cheap, fast, safe, and sensitive,11 12 allows estimates of the amount of deficits calculated from the difference in the areas between normal values or survivor values and the continuously monitored variables. Multiple noninvasive hemodynamic monitoring systems provide similar information to that of the PAC, except for pulmonary artery occlusion pressures. Discriminant analysis of these data provides a mathematical basis for outcome prediction. Future prospective clinical trials at other institutions are needed to validate the present approach.

Noninvasive monitoring also provides an approach that may be used to develop an organized coherent therapeutic plan based on physiologic criteria for the emergency patient as he/she proceeds from the ED to the OR, the radiology department, and the ICU. Linear discriminant function predicted outcome correctly in 95% of the survivors and in 62% of the nonsurvivors in the early period after hospital admission. This was probably as much as should be expected for nonsurvivors since many patients developed lethal complications unrelated to their injuries late in their hospital course.

Since the essence of tissue perfusion is an adequate supply of oxygenated blood to the tissues, perfusion is inferred from the direct measurement of skin oxygenation using the Clark polarographic method for oxygen tension.24 25 26 27 28 29 Although the skin is not representative of all tissues, it is the largest organ and the first organ to be affected by the adrenomedullary stress response. tcPO2 provides early warning in acutely ill emergency patients11 ; it tracks oxygen uptake in acute clinical shock episodes11 and in the physiologic course of experimental hemorrhagic shock24 as well as cardiac and respiratory failure, cardiac arrest, and cardiopulmonary resuscitation in acute surgical conditions.28 30 31 32 33 34 35 36 As shown in the present study, this measure of tissue perfusion was related to outcome.

In the present study, we used discriminant analysis to analyze the data of variables with p values < 0.2 in order to limit the number of variables for analysis. Interrelated or poorly conditioned variables having a common term, such as the combination of CI and oxygen delivery, were avoided to minimize statistical problems of discriminant analysis. This does not mean that the more conventional variables like tachycardia, hypotension, acidosis, skin color, lactate levels, mental status, etc, are not useful at times when they occur. Obviously, when they are abnormal, they are extremely useful and important. However, the criteria of the present study focused on early noninvasive hemodynamic variables in the immediate postadmission period that most consistently separated survivors and nonsurvivors.

The concept that hypovolemia is an early primary problem that plays an important role in low flow and poor tissue perfusion states is supported by the following: (1) direct observation of massive hemorrhage; (2) estimated blood loss of hemoperitoneum and hemothorax at the time of surgery in patients who underwent surgical exploration; and (3) prior studies in the literature that documented blood volume deficits in posttraumatic and postoperative patients who subsequently developed organ failures and died.37

Footnotes

Abbreviations: CI = cardiac index; ED = emergency department; FIO2 = fraction of inspired oxygen; GCS = Glasgow coma scale; MAP = mean arterial BP; OR = operating room; PAC = pulmonary artery catheter; SaO2 = arterial oxygen saturation; tcPO2 = transcutaneous oxygen tension

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Appendix D

List of Study Personnel Receiving Funds

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